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The utilisation of high frequency mini probe colonoscopic ultrasound in the assessment of colorectal disease

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**THE UTILISATION OF HIGH FREQUENCY MINI
PROBE COLONOSCOPIC ULTRASOUND IN THE
ASSESSMENT OF COLORECTAL DISEASE**

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**Presented for the award of Doctorate of Medicine (MD Res)
September 2012**

ABSTRACT

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This research looks at the feasibility of colonoscopic high frequency ultrasound in the colon using mini probe technology. The objectives are across four different areas with assessment of colonic cancer, malignant colorectal polyps, rectal polyps and diverticular disease

High frequency 12 and 20 MHz ultrasound were used to locally stage colonic cancer and compare this to conventional CT in patients undergoing elective colonic resection. In addition, depth of infiltration of rectal polyps was determined by 20 MHz ultrasound and these findings compared with MRI in patients undergoing TEMS procedure. Malignant colorectal polyps were assessed after endoscopic removal to assess for the presence of residual or recurrent disease in the colonic wall and also to stage the local lymph nodes. Finally, the thickness of colonic wall in patients with diverticular disease was measured using 20 MHz ultrasound and this was compared with normal controls.

The research has clearly shown that colonoscopic high frequency mini probe ultrasound is feasible in the colon with reproducible results. Overall, 12 and 20 MHz colonoscopic ultrasound are superior to CT for local staging of colonic cancer. 20 MHz ultrasound offers greater accuracy for assessment of depth of infiltration of rectal polyps compared with MRI. This probe may also be utilised to assess the colonic wall for residual disease in the polypectomy scar of malignant polyps but larger numbers are needed with longer follow up in order to draw firm conclusions. Finally, it was feasible to measure the thickness of colonic wall in patients with diverticular disease and this was greater than that seen in normal patients.

In conclusion, this research has been promising in that colonoscopic high frequency mini probe ultrasound is feasible in the colon and can be used to assess colorectal polyps and cancer and diverticular disease. In order to draw firm conclusions, this pilot research needs to be taken further with larger scale studies.

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STATEMENT OF ORIGINALITY

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The work reproduced in this thesis was undertaken the Department of Colorectal Surgery and Department of Endoscopy at Kings College Hospital, London, and is the sole work of Mr Aryn Haji.

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ABBREVIATIONS

EUS	Endoscopic ultrasound
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
MHz	Megahertz
HFUS	High frequency ultrasound
TRUS	Transrectal ultrasound
TEMS	Transanal endoscopic microsurgery
MP	Muscularis Propria
GIT	Gastrointestinal Tract
TME	Total mesorectal excision
EMR	Endoscopic mucosal resection
Sm	submucosal
ESD	Endoscopic submucosal dissection
mm	millimetre
µm	micrometres
US	ultrasound
SD	standard deviation
sem	Standard error of the mean

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CHAPTER 1

Introduction

CHAPTER 1

1.1 ENDOSCOPIC ULTRASOUND

Endoscopic ultrasound (EUS) has been used in clinical practice for over 20 years (Caletti 1986) and has been one of the most fascinating aspects of endoscopy. There have been more than 2000 papers which have been published on the use of EUS in the clinical setting not only in the Gastrointestinal Tract (GIT) but also in the lung, mediastinum and pancreas all of which have demonstrated high accuracy for the diagnosis and staging of benign and malignant conditions. At high frequencies of ultrasound, the GIT wall appears as five or more layers which correlate with the histological layers, allowing in depth examination for staging of tumours. At lower frequencies, the depth of penetration increases allowing for examination of important extra luminal pathology such as lymph nodes.

1.1.1 Principles of ultrasound

A basic understanding of the principles of ultrasound is of paramount importance for an endosonographer in order to obtain images and accurately interpret them.

Sound is mechanical energy in the form of vibrations that propagate through a medium such as air, water or tissue (Hedrick 1995). The frequency of audible sound ranges from 20 to 20 000 Hz. Ultrasound involves frequencies greater than 20 000 Hz with medical applications utilizing frequencies between 1 000 000 and 50 000 000 Hz (1-50 MHz). The propagation of ultrasound results from displacement and oscillation of molecules from their average position and then subsequent displacement and

oscillations of molecules along the direction of propagation of the ultrasound wave. The velocity of the ultrasound differs depending on the physical properties of tissue (Table 1.1). Imaging is achieved by transmitting short pulses of ultrasound energy into tissue and receiving reflected signals. The signals that return to the transducer represent the interactions of the ultrasound wave with the tissue. Any propagating wave can therefore interact with tissue and result in absorption, scattering, refraction and reflection.

Table 1.1 Physical Properties of Tissue (Duck 1990)

PHYSICAL PROPERTIES OF TISSUE		
Tissue / Fluid	Density kg/m³	Acoustic velocity m/s
Water	996	1509
Blood	1050-1075	1590
Liver	1050-1070	1578
Pancreas	1040-1050	1591
Bone	1963-2017	3760

Absorption

The absorption of ultrasound energy depends on the frequency of the ultrasound and also on the properties of the tissue medium. Higher ultrasound frequencies cause more tissue vibration and results in greater absorption.

Scattering

Individual cells, fat globules and collagen are examples of scatterers in tissue. This occurs when an ultrasound wave interacts with tissue and only a small proportion of

the acoustic intensity is reflected back to the transducer. This phenomenon occurs in tissues with heterogeneous texture and is responsible for the different images of liver, pancreas and spleen. Tissues containing fat or collagen are greater scatterers which is the reason behind the bright hyperechoic nature of the submucosal layer of the GIT.

Refraction

This occurs when the incident beam travels to the surface of the tissue at an angle other than 90 degrees, thereby causing the beam to diverge from the incident path.

Reflection

Ultrasound waves are reflected at interfaces between two media where the acoustic impedances differ. Acoustic impedance (Z) of a medium represents the resistance to sound propagating through the medium. At this interface, a proportion of the ultrasound wave is will be reflected back to the transducer and the remainder will travel through the medium. The simplest example of this is when the incident beam is perpendicular (90 degrees) to the interface.

1.1.2 Principles of ultrasound instrumentation

An ultrasound imaging system consists of an ultrasound transducer, processor and display.

The key component of any ultrasound system is the transducer. This device is initially responsible for the conversion of electrical energy to mechanical energy resulting in the transmission of an ultrasound pulse. Thereafter, upon receiving the reflected mechanical energy, it is then converted back to electrical energy and processed and

digitized by the ultrasound processor to give real time images of the tissue in question. The active element of the transducer is made from piezoelectric ceramic which are polar crystals in a specific orientation that upon application of an electrical stimulus are able to change shape (Christensen 1988).

The processor contains electronic components that are responsible for the control of the transducer, amplification of the received signal, time gain compensation and signal processing that will result in an output signal to the display.

1.1.3 EUS Equipment

Echoendoscopes are available in two different forms: radial or linear with both being available in mechanical and electronic formats. Radial echoendoscopes give circumferential views at 90 degrees to the shaft of the scope similar to the views provided by computed tomography. This similarity makes this more attractive to the majority of trainees in echoendosonography. The linear scopes, on the other hand, give views analogous to that obtained by trans-abdominal ultrasound as the view is in the same plane as scope shaft, making orientation more difficult and clinicians are easily lost during the scanning process. Therefore, for imaging of the layers of the GIT radial echoendoscopes are favoured.

Radial systems

Mechanical radial scopes produced by Olympus were for many years the standard instrument. A heavy motor in the umbilical cord of the scope drives an ultrasound transducer which sits in an oil bath at the tip of the scope beyond the oblique viewing lens (Figure 1.1). A balloon is fitted over the tip of the scope and is controlled the air

and water suction buttons housed in the scope. Once filled with water, the balloon enables acoustic coupling to the mucosa. The mechanical nature of these scopes demands care to be taken when placing or removing the balloon so that the oil bath is not damaged. Degradation of the quality of the images may be related to either a bubble developing in the balloon or is a sign that the oil bath needs refilling, a task which may need to be practised once or twice a year.

The radial systems also house a processor (for example, the EU-M20 or EU-M30). These allow for a range of frequencies to be used (5-20 MHz) and the newer models (EU M2000 or EU-M60) allow for greater focus and greater image manipulation with instant video playback.

In relation to GIT imaging, these radial echoendoscopes both mechanical and the newer electronic forms have been widely used in the evaluation of oesophageal, gastric, duodenal and pancreatic pathology. They have also been adapted for use in the rectum and distal colon. The main disadvantage for imaging in the colon is the bulky nature of the scope limiting the manoeuvres in the left colon and therefore only being able to adequately image distal sigmoid pathology.

Figure 1.1

Endoscopic ultrasound scope



Mini probes (Catheter probes)

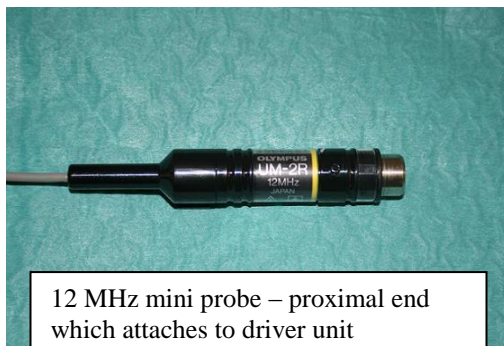
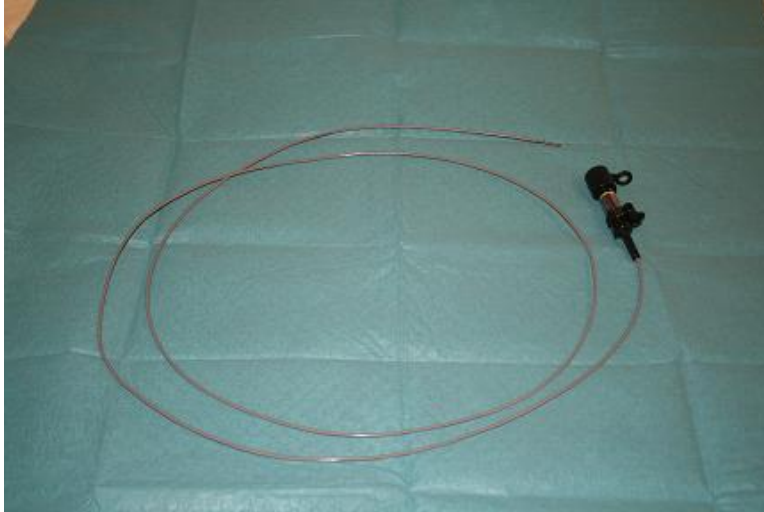
The main advantage of using mini probes to image the colon is that they are introduced through the working channel of a normal colonoscope and can therefore be used to image pathology in the left or right colon. The scope can easily be manoeuvred into the caecum during routine colonoscopy and the mini probe introduced once the pathology has been encountered.

Mini probes range in size from 2 to 2.6 mm and are mechanical radial probes which require an additional small motor drive unit between the probe and the ultrasound transducer (Figure 1.2 and 1.3). The probes are usually of high frequencies ranging from 12 to 30 MHz (UM-2R 12 MHz, UM-3R 20 MHz and UM-S30-25R 30 MHz)

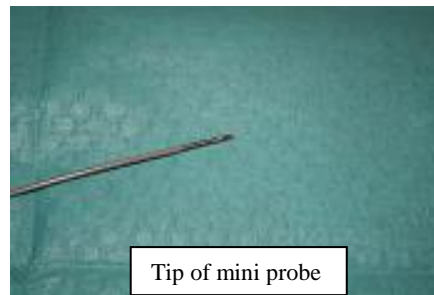
with the highest frequencies offering only a shallow depth of view suitable for imaging small mucosal and subepithelial tumours. One particular technical issue with the mini probes is the difficulty on occasion of excluding air from the site. After suctioning of the air from the site under interrogation, water flooding of the colon is required for acoustic coupling. Balloon sheaths are also available for the mini probes but these will require the use of colonoscopes with large calibre working channels.

The mini probes are not single use and undergo similar cleaning and sterilization to the endoscopes. However, due to their fragility, one must exercise caution if the full lifespan of 35-50 procedures is expected.

Figure 1.2 High frequency mini probe ultrasound



12 MHz mini probe – proximal end
which attaches to driver unit



Tip of mini probe

Figure 1.3 Motor drive unit and display screen for the mini probe ultrasound



Motor drive unit for mini probe

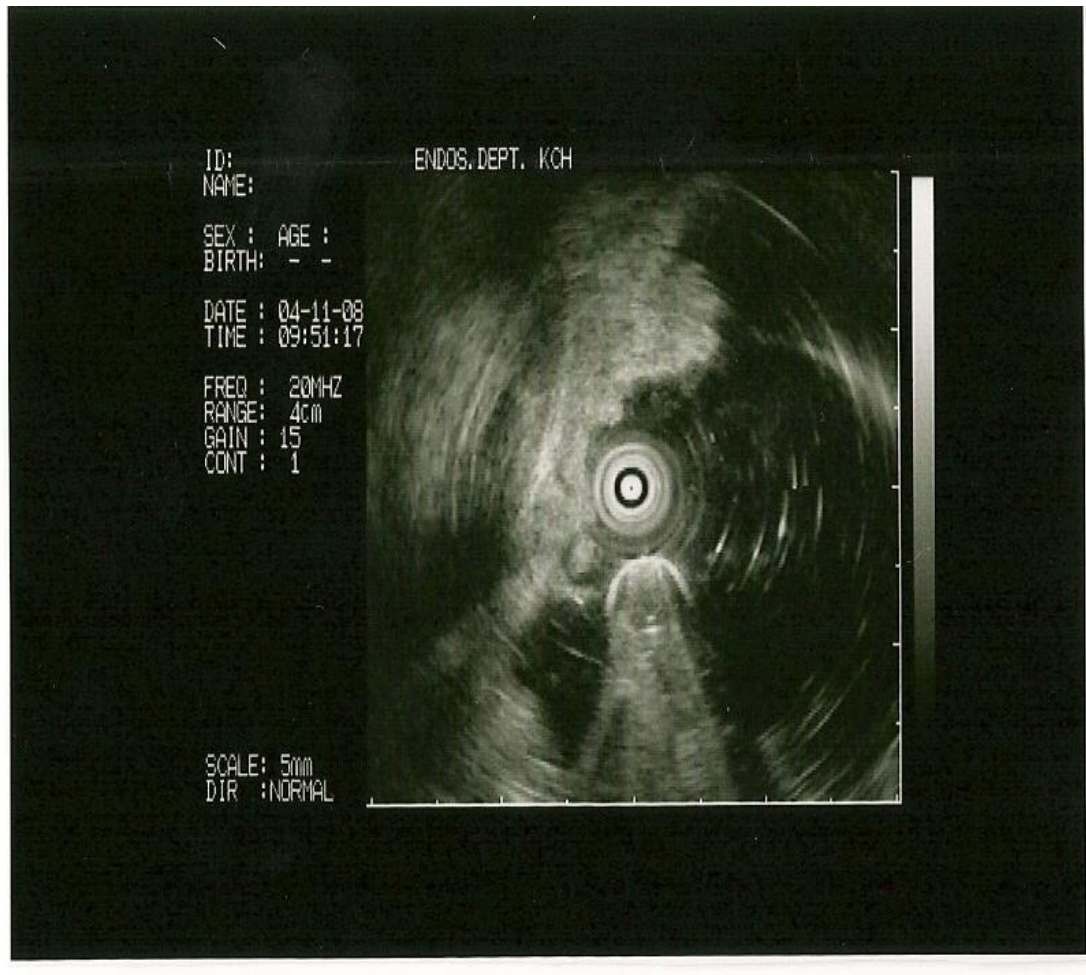
1.1.4 Imaging artefacts

The interpretation of ultrasound images improves with experience and a thorough understanding of imaging artefacts which do not represent the tissue being examined is vital. There are some common artefacts which are explained as these patterns are important to recognise especially when accurately staging GIT cancers.

Reflection

This is a common finding during colonoscopic ultrasound as a mirror image appears as an artefact when ultrasound is undertaken near an air-water interface such as that which occurs when the lumen is partially filled with water. The ultrasound pulses reflect off the air-water interface due to impedance mismatch creating a mirror image of the pathology opposite the air-water interface (Figure 1.4)

Figure 1.4 **Reflection (mirror image) artefact with an image of the transducer and the colonic wall produced by reflection of the ultrasound signal from the air-water interface in the colonic lumen**



Acoustic shadowing

This form of reflection artefact may occur when there is a significant impedance mismatch. Therefore the majority of the transmitted ultrasound pulse is reflected with minimal transmission through the tissue. The resulting image is hyperechoic at the interface and a shadowing beyond the interface due to lack of detection of an echo signal. A classic example of this effect is demonstrated in the imaging of gallstones, but in the GIT this may occur when interface is curved such as that seen with a large tumour (Figure 1.5)

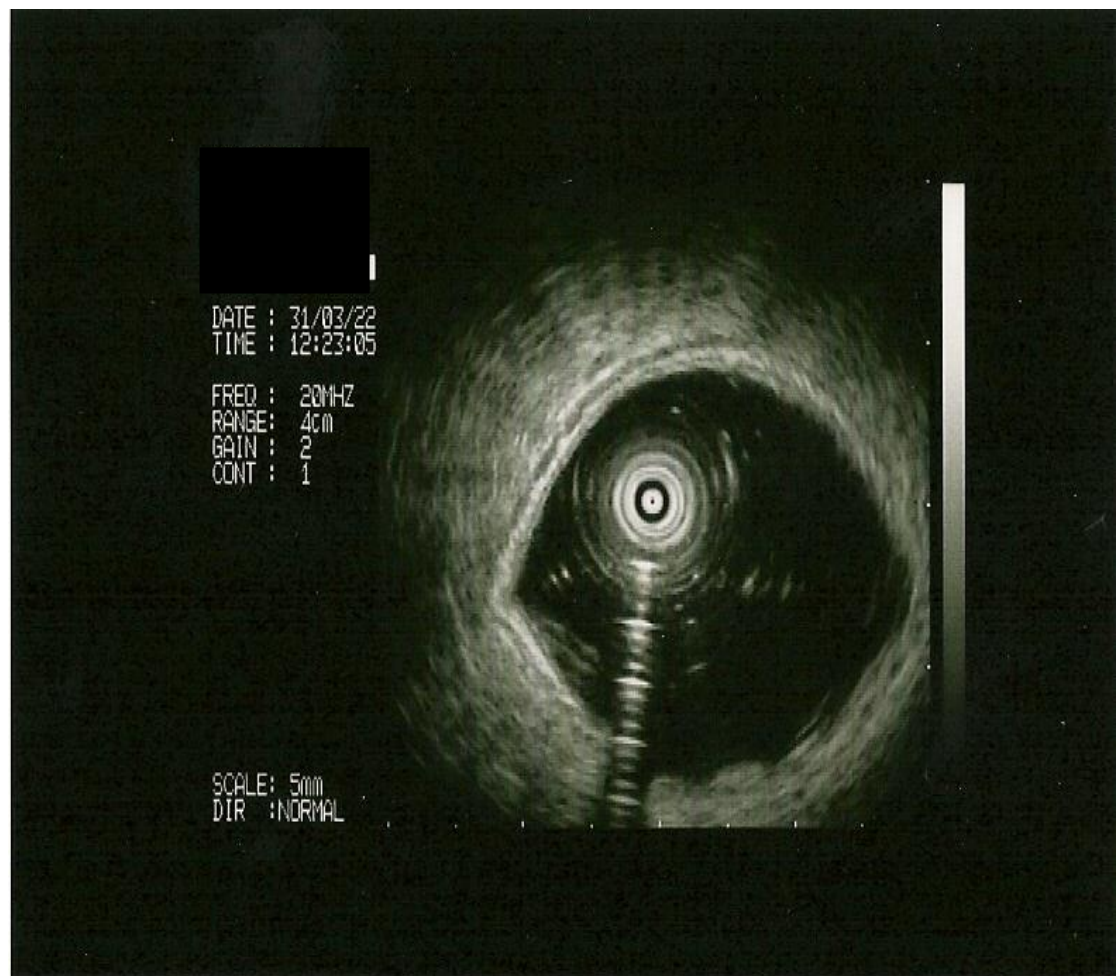
Figure 1.5 **Acoustic shadowing resulting from the refraction between normal tissue and tumour**



Reverberation

This ring effect is important to recognise as it may be easily rectified with some technical adjustments. This occurs when a transmitted pulse undergoes multiple reflections. The pulse is bounced to and fro from the reflector to the transducer and back multiple times, which produces equally bright bands. The two common reasons for this artefact are from the housing of the ultrasound transducer or from small air bubbles (Figure 1.6).

Figure 1.6 Image of reverberation from an air bubble. Note the multiple bright or hyperechoic bands produced by multiple reflections.



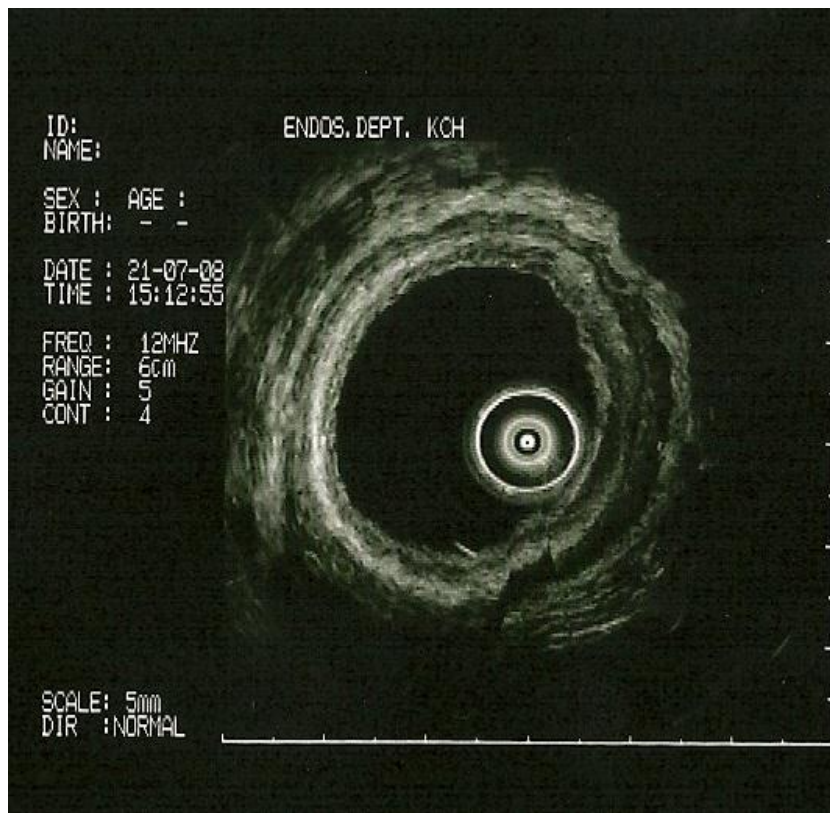
Tangential scanning

The assessment of the layers of the GIT requires the ultrasound probe to transmit pulses perpendicular to the gastrointestinal wall. This is crucial when staging cancers of the GIT or during measurement of the thickness of the wall. If the ultrasound transducer is at an angle other than that of 90 degrees to the pathology in question, then this may result in over staging the tumour or overestimation of the thickness.

1.2 ENDOSCOPIC ULTRASOUND AND STAGING OF GASTROINTESTINAL TUMOURS

The aetiology of the majority of tumours in the GIT can be determined by the appearance on endoscopy and endoscopic ultrasound with histological confirmation of the diagnosis in question. The advantage of radial endoscopic ultrasound is that it is able to visualise the different layers of the gut wall as distinct entities comparable to that of histological layers. This is seen as a series of concentric rings of differing echogenicity. On classic 7.5 or 12 MHz endoscopic radial ultrasound imaging, the first 2 layers are hypoechoic which corresponds to the mucosa and muscularis mucosae. The 12 MHz ultrasound does not differentiate between these 2 layers as they are both hypoechoic. The third layer is hyperechoic and is the submucosa. The echoic layers alternate as you traverse through the gut wall thereby demonstrating the fourth layer as hypoechoic (muscularis propria) and the fifth serosal layer as hyperechoic (Figure 1.7).

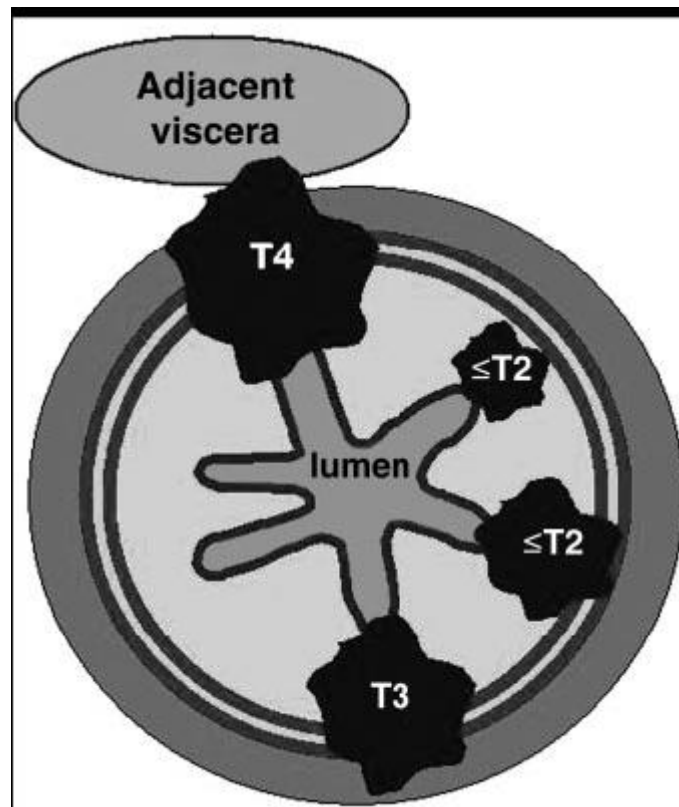
Figure 1.7 The layers of the gut wall on radial 12 MHz endoscopic ultrasound



Accurate staging of tumours in gastrointestinal tract is crucial for optimal patient care and gives a good indication of survival. Tumours are staged according the American Joint Committee on Cancer TNM classification (AJCC 1977) which describes the anatomical extent of the cancer. The T stage is related to the depth of invasion of the tumour through the gut wall; the N stage refers to the presence or absence of lymph nodes locally; and distant metastases are depicted by the M stage. The purpose of endoscopic ultrasound is to determine the T and N stage of tumours. The T stage of tumours for oesophageal, rectal and colonic cancers are shown in more detail using a schematic (Figure 1.8). Both benign and malignant lymph nodes are visualised with endoscopic ultrasound and there are certain features which point towards malignancy being more likely. These include the lymph node having a short axis diameter greater

than 5mm, round shape, distinct outer border and hypoechoic features (Bhutani 1994, Catalano 1997).

Figure 1.8 Schematic diagram detailing the T stage of gastrointestinal tumours



Inner dark circle=muscularis mucosae; outer dark circle= muscularis propria

1.2.1 Lessons from oesophageal cancer staging

Oesophageal cancer is a global health problem with nearly 15000 patients diagnosed with the disease in the United States each year, of whom nearly 14000 will succumb to their illness (Jemal 2005). Despite the improvements in the management over the last decade, overall 5 year survival rates remain poor. The outcome of patients with oesophageal cancer is dependent on stage and endoscopic ultrasound plays a major role in the decision making process. T1 and T2 tumours without evidence of local lymphadenopathy would typically go for primary surgical resection, whereas those

with any nodal disease or locally advanced cancer (T3 or T4) would receive neoadjuvant treatment in the form of chemotherapy with or without radiotherapy.

The accuracy of EUS in the assessment of T stage of oesophageal tumours is far superior to that of CT imaging. Two metaanalyses by Rosch et al 1995 and Lightdale et al 2005 have shown an accuracy of 85-90% for EUS compared with 50-80% for CT. In addition, EUS is also superior in the detection of local lymphadenopathy, both peritumoural and coeliac. Both Rosch (1995) and Kelly and colleagues (2001) have revealed that nodal staging for EUS has an accuracy of 75-79% considerably better than that obtained by CT (Table 1.2)

Table 1.2 Staging of oesophageal cancer – A comparison of EUS and CT

STAGING ACCURACY OF OESOPHAGEAL CANCER		
Imaging	T stage (%)	N stage (%)
EUS	85 (59-92)	77 (50-90)
CT	45 (40-50)	54 (48-71)

(Rosch 1995)

The studies in the literature quoted used traditional echoendoscopes rather than mini probes. The latter have the added advantage of traversing constricting tumours of the oesophagus which may be inaccessible to traditional EUS.

1.2.2 Rectal Cancer

1.2.2.1 Background

Colorectal cancer is the third commonest cancer worldwide (Jemal 2005) and the second cause of cancer related deaths in the Western world. The development of cancer from adenomatous polyps is well recognised; a process which may develop over 10-15 years termed the adenoma-carcinoma sequence (Vogelstein 1988). Rectal cancers account for 30-40% of all cancers in the large bowel. It is defined as tumours within 15cm of the anal verge on rigid sigmoidoscopy and anatomically the rectum begins where the two antimesenteric taenia on the sigmoid colon fuse together. The distance from the anal verge helps to classify the tumours into upper third, middle third and lower third according to the International Union Against Cancer (UICC).

The mesorectal fascia is an important anatomical landmark for the evaluation of local tumour spread. This connective tissue sheath forms an envelope around the rectum and perirectal fat including lymph nodes and behaves as the natural barrier to for cancer spread. Modern imaging techniques are able to visualise this fascia and the relationship to the tumour margins. In addition to the mesorectal fascia, the other import factors responsible for determining prognosis and local recurrence are the depth of invasion of the tumour into the rectal wall (T stage) and the presence or absence of lymph node invasion (N stage) (Table 1.3) Historical data shows that if the tumour is confined to the mucosa and submucosa with no evidence of lymph node involvement, the local recurrence risk is 5%. This increases to 10% if the tumour invades the muscularis propria (T2 tumour), 25% if the tumour extends into the perirectal fat (T3) and 50% if adjacent structures are involved (T4) (Chapuis 1985, Fielding 1989, Hermanek 1989).

Table 1.3 **TNM staging in rectal cancer** (Sobin 2002)

TNM STAGING IN RECTAL CANCER	
T1	Mucosal involvement (T1m) Submucosal involvement (T1sm)
T2	Invasion into muscularis propria
T3	Invasion through and beyond muscularis propria
T4	Adjacent structures involved
N0	No local lymph nodes involved
N1	1-3 perirectal nodes
N2	≥ 4 perirectal nodes
M0	No metastases
M1	Distant metastases

There are several factors that determine the best treatment strategy employed in patients with rectal cancer including tumour location, T and N stage and grade of tumour. The local recurrence rates even after curative resection of the rectum vary from as low as 2% up to 32% (Sagar 1996). Lateral circumferential extent of the cancer is more important as a prognostic indicator for local recurrence than longitudinal tumour extent (Quirke 1986, Adam 1994, Martling 2003). Quirke and colleagues have shown that patients with positive microscopic margins have local recurrence rates as high as 83% (Quirke et al 1986). Local recurrence is debilitating and has a great impact of the quality of life of patients, therefore paramount attention has been given to the decision making enabling appropriate selection of patients for primary surgery or neo-adjuvant chemo-radiation prior to surgical resection.

Therapeutic options for rectal cancer

Since the introduction of total mesorectal excision (TME) (Heald 1982), few surgeons doubt the advantages of performing rectal resection along with complete excision of the mesorectum. Standardised TME for patients with low or mid rectal cancer involves resection of the rectum along with the surrounding lymphatics, nodes, fatty tissue and mesorectal fascia sparing the pelvic splanchnic nerves and the parietal pelvic fascia. There is some debate whether this technique should be employed for high rectal cancers or whether rectal resection should be undertaken with 5cm of distal clearance.

In any case, primary surgical treatment would be reserved for patients with early cancer (T1, T2 without nodal involvement) with the introduction of neo-adjuvant chemo-radiation to downstage locally advanced cancers (T3, T4) to facilitate curative resection and prevent local recurrence. In 1990, the National Institutes of Health Consensus Conference recommended that patients with locally invasive rectal tumours (T3, T4, TxN1-2) should receive neo-adjuvant treatment. This reflected the findings of the Swedish Rectal Cancer Trial (1997) showed that a short cycle of preoperative radiotherapy reduces the local recurrence rate from 27% to 11%. Kapiteijn et al (2001) further showed that local recurrences rates were lower also in patients who had both TME and neo-adjuvant radiotherapy compared to the TME only group.

The complexity of decision making in the management of rectal cancer re-iterates the importance of accurate staging of rectal tumours to decide whether primary surgery or whether neo-adjuvant treatment should be employed. Within this context, it goes without saying that it is of paramount importance to avoid either over treating or undertreating patients. Three imaging techniques are now available for staging the primary tumour: transrectal endoscopic ultrasound (TRUS), computerised tomography

(CT) and magnetic resonance imaging (MRI). There have been many studies reporting on imaging for rectal cancer and most focus on T and N stage with a few discussing the circumferential resection margin.

1.2.2.2 Transrectal ultrasound (TRUS)

Transrectal ultrasound was first introduced in clinical practice for local staging of rectal cancer in 1985 (Hildebrandt 1985) and the application of TRUS has expanded in the last decade. Since then, there have been several studies to determine the accuracy of TRUS and compare this to other imaging modalities. Skandarajah et al (2006) evaluated all the studies from 1984-2005 and discovered 867 articles in the medical literature. The most commonly used equipment in the literature is the rigid 7 MHz rotating endorectal probe providing a 2D image in a 360 degree axis with a focal length of 2-5cm (B&K ultrasound machine, Type 3535, Naerum , Denmark). The utilisation of the 7, 7.5 or 12 MHz endorectal ultrasound probe presents the bowel wall in five sonographic layers as a result of differing acoustic impedance (Figure 1.7). The ultrasound staging of tumour depth is prefixed by “u” but corresponds to the TNM staging (Table 1.4).

Table 1.4 Ultrasound staging for depth of invasion of tumour

ULTRASOUND STAGING IN RECTAL CANCER	
uT1	Tumours confined to mucosa and submucosa
uT2	Invasion into muscularis propria
uT3	Invasion through and beyond muscularis propria into perirectal fat
uT4	Adjacent structures involved

A systematic review was conducted to identify the accuracy of transrectal ultrasound in the T and N staging of rectal tumours. Skandarajah et al (2006) conducted a similar review and identified 31 studies in the literature which contained more than 50 patients and also clearly compared TRUS to histological staging. The period included in their study span from 1984-2004. A further seven studies were identified with similar criteria after extending the search period to 2008.

Accuracy of T staging

The accuracy of T staging for rectal cancers using TRUS varies from 63.3% to 96%, with an overall accuracy of 83.8% for all stages. (Table 1.5) This series of different studies in the literature holds a total of 8357 patients. The accuracy of TRUS varies with stage with individual tumour accuracies being: T1-73.2% (40-100%); T2-70% (12-96%), T3-87.6% (56.8-100%); and T4- 75% (25-100%). Most of the studies have high accuracies but the overall result was influenced by 3 large studies (Ptok 2006, Garcia-Acguilar 2002, Marusch 2002) with large numbers of patients and accuracies of 63.3, 69 and 65.8% respectively.

Harewood et al (2002) prospectively evaluated 80 patients with rectal cancer using TRUS and reported T staging accuracy of 91%. The authors showed that the utilisation of transrectal ultrasound altered the management in nearly a third of the patients enabling upstaging of T stage and therefore neo-adjuvant treatment. In contrast, only 5 out of 33 patients with T3 stage were under staged and therefore went straight to surgery, all of whom required post-operative chemo-radiotherapy. Halefoglu and colleagues (2008) also showed high accuracy rates for T staging of rectal cancer with 85.3% accuracy in 34 patients. The sensitivity and specificity of TRUS was reported as 70.6%

and 90.2% respectively. However, in their smaller series, TRUS under staged 4 patients with T3 tumours and over staged 5 T2 tumours as T3, thereby giving an overall accuracy of discriminating between pT1-pT2 and pT3-pT4 tumours of 76.5%, with a 87.5% sensitivity and 50% specificity. This is consistent with the staging errors seen in the literature with the most common being that of over staging T2 as T3.

The discrepancies seen in the accuracy between the studies can be explained by several factors. Firstly, many of the earlier studies were done by inexperienced ultrasonographers and there is a recognizable learning curve with TRUS. Both Carmody et al (2000) and Lohert et al (2000) have independently shown that the ultrasonographers improved their accuracy rates from 58% to 95% over time, after 24 patients in the first study and after 3 years' experience in the second group. Secondly, morphology of the rectal tumour may hinder the examination as bulky tumours or those after biopsy, local excision and radiotherapy may provide inadequate images. Haemorrhage after biopsy or local excision can obliterate the layers seen on ultrasound and the desmoplastic reaction and hypervascularity after radiotherapy tend to lead to over staging of the tumours. Despite the discrepancies, one common fact is that T2 tumours are regularly staged incorrectly. There is technical difficulty in differentiating between invasion into the muscularis propria and invasion through the muscularis propria into the perirectal fat. Thus, there is a tendency to overstage these tumours. The peritumoural inflammation changes the appearance of the rectal wall making an hyperechoic layer look hypoechoic. This would in turn lose the outer hypoechoic layer displaying a T2 tumour as a T3 or T4 tumour (Katsura 1992).

TRUS has been shown to be more suitable for early tumours rather than advanced tumours as the modality is unable to visualise the mesorectal fascia and predict the circumferential margin due to the limited focal length. The focal length of a 7.5 MHz transducer reaches up to 5cm only, therefore tumour or lymph nodes further away than this distance cannot be visualised. Solomon et al (1993) in their metaanalysis showed that early tumours were staged more accurately than more advanced tumours. On the other hand, Puli and colleagues (2009), in their meta-analysis containing 5039 patients showed higher pooled sensitivity and specificity for the more advanced T stages of rectal cancers. For T1 stage, pooled sensitivity and specificity were 87.8% and 98.3% respectively; for T2 – 80.5% and 95.6%; for T3 – 96.4% and 90.6%; and for T4, TRUS had a pooled sensitivity and specificity of 95.4% and 98.3% respectively. Although there is great variation in the sensitivity of T staging in the literature, TRUS overall as a diagnostic staging test has a high diagnostic odds ratio especially for early T stages and therefore enables clinicians to offer surgical treatment alone with confidence to patients with early disease.

Accuracy of N staging

TRUS nodal staging is less accurate than that of T staging and accuracies range from 50% to 86%. Table 1.6 shows the main studies from the literature and gives an overall accuracy of 71.4% in 3712 patients assessed for nodal disease. Such wide variations in accuracies exist in the literature as authors use variable criteria for defining nodal metastases. Historically, the main characteristics of malignant nodes include a round shape, peritumoural location, hypoechoic appearance and size greater than 5mm.

Beynon et al (1986) showed that nodes greater than 5mm have a 50-70% chance of harbouring metastases whereas nodes less than 4mm have only a 20% chance. Hildebrandt and colleagues (1986), on the other hand, did not use size as a criterion but relied only on echogenicity relying on the observation that inflammatory nodes are hyperechoic and malignant ones are hypoechoic in nature. This statement holds independent of size as that is thought to be a poor indicator of malignancy. Katsura and colleagues (1992) showed that although 53.8% of nodes greater than 5mm were histologically cancerous, 72.3% of nodes with hypoechoicity harboured metastases. Spinelli et al (1999) also showed that the sensitivity of TRUS was significantly lower once nodes were less than 5mm. Although TRUS can identify nodes as small as 3mm but it is unable to identify whether micrometastases are present at that size as the architecture of the nodes are not greatly altered (Kim 2000). Gleeson and colleagues (2009) felt that nodal echo features alone are often inadequate to establish the presence of loco regional metastatic disease and recommended further evaluation by fine needle aspiration of the nodes in question. Conventional ultrasound features of malignant nodes include 4 factors: smooth, round, hypoechoic and greater than 10mm nodes. However, in their series only 68% of malignant nodes had more than 3 of these features. Non-conventional criteria were evaluated and short axis length >5 mm, in addition to the conventional hypoechoic feature, were the only factors independently predictive of malignancy.

Puli et al (2009) conducted a meta-analysis on the accuracy of transrectal ultrasound to diagnose nodal invasion by rectal cancers. They identified 35 relevant studies with 2732 patients. The pooled sensitivity and specificity of diagnosing nodal involvement by transrectal ultrasound was 73.2% and 75.8% respectively. Interestingly, TRUS had

a low negative likelihood ratio of 0.42 and a higher positive likelihood ratio of 2.84 which translates to TRUS performing better to exclude nodal invasion by rectal cancer when compared with the ability to confirm nodal invasion.

Table 1.5 Accuracy of T staging using TRUS

Author	No. Patients	T1	T2	T3	T4	Overall Accuracy (%)
Jargenson 2011	83	NR	NR	NR	NR	76
Ju 2009	78	100	84	81.8	84.6	84.6
Halefoglu 2008	34	NR	NR	NR	NR	85.3
Badger 2007	95	87.5	12	96.6	33.3	71.6
Ptok 2006	3501	59	59.6	74.9	31.1	65.8
Maor 2006	66	54.5	85.7	95	100	86
Knaebel 2005	424	NR	NR	NR	NR	81.8
Knaebel 2005	332	NR	NR	NR	NR	71.8
Kauer 2004	458	52	59	86	36	69
Mackay 2003	433	85.7	65.6	77	89.2	89
Nesbakken 2002	81	40	81	80	25	74
Garcia-Aguilar 2002	545	47	68	70	50	69
Marusch 2002	422	50.8	58.3	73.5	44.4	63.3
Harewood 2002	80	NR	NR	NR	NR	91
Akasu 2000	154	96.5	96	96	96	96
Palacios 2000	120	100	44	96	100	90
Kim 1999	89	100	50	87	71	81.1
Massari 1998	75	86.6	88.8	91.4	100	90.7
Fedyaev 1995	109	NR	94	87	93	95
Hulsmans 1994	55	50	80	56.8	75	60
Herzog 1993	111	86	65	99	100	89
Katsura 1992	112	100	95	87	100	92
Milsom 1992	67	NR	NR	NR	NR	85
Tarroni 1992	214	NR	NR	NR	NR	94
Tio 1991	61	72	47	97	50	80
Glaser 1990	86	80	77	100	89	88
Jochem 1990	50	76	76	92	92	80
Orrom 1990	77	71	69	92	100	75
Beynon 1989	100	NR	NR	NR	NR	93
Hildebrandt 1986	76	50	76	100	100	88
Rifkin 1986	81	NR	NR	NR	NR	84
Saitoh 1986	88	93	93	92	75	90
OVERALL	8357					83.8

NR = not recorded

Table 1.6 Accuracy of N staging using TRUS

Author	No. Patients	Overall accuracy (%)
Jargenson 2011	83	63
Ju 2009	78	64.1
Halfoglu 2008	34	76.5
Badger 2007	95	68.8
Ptok 2006	NR	NR
Maor 2006	66	71
Knaebel 2005	424	76
Knaebel 2005	332	71
Kauer 2004	NR	NR
Mackay 2003	263	66
Nesbakken 2002	81	65
Garcia-Aquilar 2002	545	72
Marusch 2002	111	80
Harewood 2002	80	82
Akasu 2000	154	72
Palacios 2000	120	70
Kim 1999	89	63.5
Massari 1998	75	76
Fedyaev 1995	72	61.1
Hulsmans 1994	54	52
Herzog 1993	111	80.2
Katsura 1992	98	61.2
Milsom 1992	NR	NR
Tarroni 1992	84	84
Tio 1991	214	70
Glaser 1990	61	80
Jochem 1990	73	72
Orrom 1990	50	82
Beynon 1989	75	83
Hildebrandt 1986	27	50
Rifkin 1986	81	86
Saitoh 1986	71	73
OVERALL	3712	71.4

1.2.2.3 Magnetic Resonance Imaging (MRI)

MRI has been used to evaluate rectal cancer since 1986 (Hodgman 1986, Butch 1986). Initially, the accuracy of T staging of rectal cancers was disappointing and similar to that of Computerised Tomography with accuracies reported between 59% to 74% (Butch 1986, Cova 1994, Zerhouni 1996). The main problem faced with conventional external body coil techniques is that it is difficult to differentiate the layers of the rectal wall accurately giving poor spatial resolution. Endorectal coils were therefore popularised and this imaging technique produced T staging accuracies comparable to that of TRUS with 80-90% accuracy stated in many studies (Chan 1991, Schnall 1994, Vogl 1997, Gualdi 2000). The high accuracy rates were the result of high resolution and differentiation of the layers of the rectal wall. However, this comes at the expense of several difficulties encountered when using the endorectal coils. They are often too large to pass beyond bulky tumours and stenotic lesions with appropriate positioning often being difficult (Matsuoka 2003). The balloon distension required may also distort the rectal wall (Bartram 2002). An important limitation is that the mesorectal fascia and the assessment of the circumferential margin is limited as there is a radial signal drop off giving a diminished field of view only a short distance from the endorectal coil (Beets Tan 2004). In addition, endorectal coils are not only limited in availability but also expensive being single use items.

The new generation of external high resolution phased array surface coil systems has improved the local staging of rectal cancer. The combination of high resolution, improved signal to noise ratio and a large field of view allows detailed anatomical evaluation of the rectal wall and mesorectal fascia (Table 1.7). Despite these advantages, overall T staging accuracies of recent studies vary from 67-86% which is

disappointing (Bloomqvist 1997, Beets-Tan 2001, Gagliardi 2002, Poon 2005). These results can be attributed to the fact that MRI fails worse at staging T1 and T2 tumours than more advanced cancers. Mathur et al (2003) showed that T1 and T2 tumours were staged to an accuracy of 46% whereas T3 tumours were at 76%. Similar observations were made by Drew et al (1999) and Hadfield and colleagues (1997).

The majority of clinicians would now argue that the most important question relating to MR imaging and rectal cancer is the relationship of the tumour to the mesorectal fascia. This is of vital importance as the surgical resection in the form of TME would only be primarily undertaken if there is a clear margin between the tumour and the mesorectal fascia. The importance of predicting this tumour free circumferential resection margin (CRM) has been highlighted in recent MR studies using phased array surface coils. Beets-Tan et al. (2001) assessed 76 patients with rectal cancer using phased array coil MRI at 1.5 Tesla and predicted not only tumour stage but also distance from the tumour to the mesorectal fascia. On MR imaging the mesorectal fascia is a fine linear structure enveloping the mesorectum being hypointense on T2 weighted and isointense on contrast enhanced T1 weighted images. They showed that the CRM can be predicted with high accuracy and consistency with 2 radiologists. Agreement between the 2 radiologists was 100% in T4 tumours, and 97% and 93% for the two radiologists in patients with tumours with a histological CRM of greater than 10mm. For margins of 1-10mm, a tumour free CRM of 2mm was predicted with an accuracy of 97% if the distance between the tumour and the mesorectal fascia was at least 6mm. It is interesting to note that in this same study, the accuracy of MR staging of rectal cancer was only 67% for the first radiologist and 87% for the second. Furthermore, the accuracy for staging T1 and T2 tumours were markedly lower (38%

and 42%) than that of T3 and T4 tumours (95% and 100%). Certainly for the earlier stage tumours, there was no agreement between the two radiologists. The difficulties with staging T2 tumours for this group was thought to be poor distinction of speculation in the perirectal fat caused by fibrosis only (T2) from that caused by cancerous cells (T3). This is in complete contrast to the work by Brown and colleagues (1999) correctly staged 100% of rectal tumours and visualised the mesorectal fascia in all of their 25 patients. They felt that peritumoural fibrosis had a distinct lower signal intensity compared to that seen in cancerous margins.

Although tumour staging using the T stage of the TNM classification is the traditional method of prognostically stratifying patients, this method has its limitations. In particular, the majority of rectal cancers at presentation are T3 tumours and the outcomes of these patients depend on the depth of extramural spread. The University of Erlangen group have published one of the largest series of rectal cancers (Merkel et al 2001) and showed that T3 tumours with extramural spread greater than 5mm were associated with a cancer specific 5 year survival of 54% compared with that of 85% seen in those T3 tumours with less than 5mm of extramural spread, regardless of whether lymph node involvement was present.

The MERCURY (Magnetic Resonance Imaging and Rectal Cancer European Equivalence) Study group is a multidisciplinary collaboration formed in 2002 for the prospective evaluation of preoperative assessment in patients with rectal cancer. The group assessed the accuracy of preoperative staging of rectal cancer with MRI to predict surgical circumferential margins in 2006. The specificity for prediction of a clear margin by MRI was 92% with an accuracy of 91% and a negative predictive

value of 93% in patients undergoing primary surgery. In 2007, the group evaluated MRI versus the histopathological measurement of extramural depth of tumour invasion. Data was available for 295 patients of the 311 patients that underwent primary rectal cancer surgery. They demonstrated highly accurate measurement of the depth of extramural tumour spread as MR and histopathological assessments of tumour spread were equivalent to within 0.5mm. The same group have reported their 5 year follow up (Taylor et al 2011) and demonstrated that of the 374 patients who completed follow up, 33% were classified as good prognosis initially with either clear surgical circumferential margins or less than 5 mm spread from the muscularis propria. The 5 year overall and disease free survival for this good prognosis group was 68% and 85% respectively . Furthermore, this group had a low local recurrence rate of only 3%.

Several other authors have also shown good results with MRI and rectal cancer. Akasu and colleagues (2009) showed excellent agreement of T stage in 85 out of 101 rectal cancer patients (84%). This high accuracy was maintained across the T stages with 96%, 88% and 99% for T2, T3 and T4 stages respectively. In addition, they showed 96% accuracy for detection of mesorectal fascia involvement and 74% overall accuracy for detection of lymph node metastasis. Halefoglu et al. (2008) showed superior staging using MRI in 34 patients with rectal cancer. They achieved 89.7% accuracy in T staging of rectal cancers for MRI, with a sensitivity of 79.4% and a specificity of 93.1%. Equally, detection of lymph node metastases achieved an accuracy of 74.5%. Overall MRI had a 85.2% accuracy in discriminating between pT1-pT2 and pT3-pT4 tumours, with MRI over staging 4 pT2 cases as T3 similar to the over staging seen with TRUS in the same study.

Table 1.7 Layers of the rectal wall as seen with MRI
(Bartram and Brown 2002)

LAYERS OF THE RECTAL WALL ON MRI	
1	Mucosa: thin, low intensity signal
2	Submucosa: thicker, higher intensity signal
3	Muscularis Propria: low signal intensity
4	Perirectal fat: high signal intensity
5	Mesorectal fascia: fine low signal intensity enveloping the rectum

The identification of positive local lymph nodes in rectal tumours are the most challenging for an imaging modality as micrometastases can occur in normal size lymph nodes. Accurate staging is vital as the number of lymph nodes affect prognosis as well as the proximity of lymph nodes close to the mesorectal fascial envelope. The problems encountered with TRUS are also valid for MRI as size of lymph nodes is not an important criterion for metastatic disease. Brown et al (2003) showed that in lymph nodes greater than 3mm, factors such as an irregular border and mixed signal intensity are better than using size alone. Kim and colleagues (1999) re-iterated the importance of using multiple criteria to assess lymph nodes rather than size alone. The consequences of the difficulty in assessing nodes have given rise to the wide variation in accuracies for nodal staging with MRI ranging from 39% to 95% (Table 1.8).

Table 1.8 Accuracy of N staging in rectal cancer using MRI

Author	No. Patients	Overall accuracy (%)
Hodgman 1986	34	39
Butch 1986	16	37.5
De Lange 1990	23	57
Okizuka 1993	33	87
Schnall 1994	36	81
McNicholas 1994	20	95
Thaler 1994	37	60
Indinnimeo 1996	23	78.9
Kwok 2000	4897*	65
Halefoglu 2008	34	74.5
Akasu 2009	101	74

*systematic review

Over the last few years, the use of ultrasmall superparamagnetic iron oxide (USPIO) has been suggested as a method of improving the nodal staging accuracy with MRI. The particles are phagocytosed by macrophages in lymph nodes and result in decreased signal intensity in normal nodes. This should in turn increase the detection of micrometastases. Koh et al. (2004) used USPIO-enhanced MRI and reported an association of lymph node enhancement with metastasis. Lahaye et al. also assessed 28 rectal cancer patients with USPIO-enhanced MRI and compared accuracy of several criteria for predicting mesorectal node involvement, including border irregularity, short- and long-axis diameter, and estimated white region percentage. They reported that estimated white region percentage to be reproducible, accurate and practical. This should be the basis of a future prospective study in a larger cohort.

1.2.2.4 Computerised Tomography

The advantage of CT is that it enables visualisation of the entire abdomen and pelvis and is valuable for detection of distant metastases. The initial reports of CT staging of

rectal cancer depth were promising in the literature with accuracy rates of 90% (Theoni 1981, Zaunbauer 1981). However, the majority of these patients had advanced tumours. The more recent studies have T staging accuracies ranging from 47% to 75% (Freeny 1986, Bech-Shriver 1992). The main difficulty with CT imaging is that it is unable to differentiate the different layers of the rectal wall. Therefore, this makes it challenging to differentiate between T1 and T2 tumours and most of the studies with high accuracies have a small percentage of T1 tumours. In addition, it is also not possible to differentiate between inflammation and cancerous margins and the identification of the mesorectal fascia with good resolution which is vital to the management decisions in rectal cancer. Kwok et al (2000), in their metaanalysis of 78 studies from 1980 and 1998 included 4897 patients and showed that the T staging accuracy with CT for rectal cancer was 73%. Conventional CT protocols with low spatial and contrast resolution with thick slice CT accounted for these poor results. The newer generation multi-slice CT scanners with reconstructions in multiple planes have produced more promising data. Kulinna and colleagues (2004) showed an accuracy of 86% in a study of 92 patients. These achievements were confirmed by Fillipone et al (2004) who showed accuracy for T staging of 83% in 41 patients.

Lymph nodes, when enlarged can be visualised by CT but it is not possible to differentiate between reactive or inflammatory nodes and those infiltrated by cancer. Some authors have tried to define malignant nodes with respect to their size but this has not been reliable and results vary considerably.

1.2.2.5 Summary

The review of the literature to date has shown that local staging of rectal cancer should be undertaken by TRUS and MRI. However, it seems that TRUS provides more accurate staging for early cancers (T1 and T2), whereas MRI is superior for more locally advanced tumours. Both imaging modalities offer similar accuracies in nodal staging. MRI has a clear advantage for predicting tumour free CRM as this is not clearly visualised by TRUS. CT imaging is not appropriate for local staging currently but studies with the new generation multi-slice scanners are eagerly awaited.

1.2.3 Colonic Cancer

1.2.3.1 Background

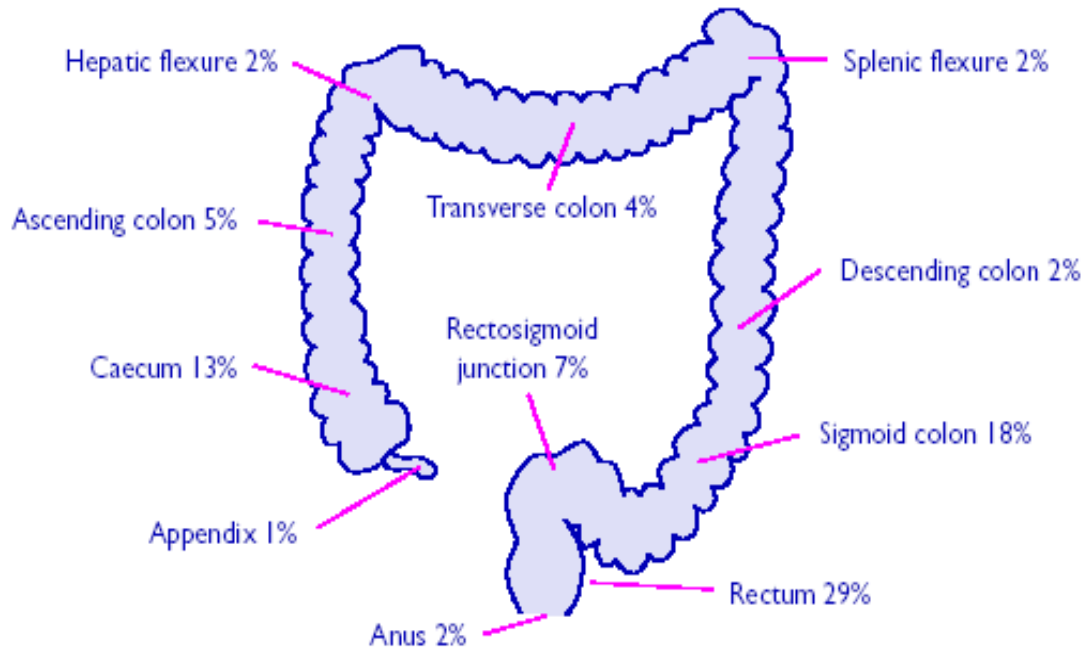
Colorectal cancer is the third commonest cancer worldwide after lung and breast cancer with over two thirds of cancers occurring in developed nations. In excess of a million new cases of colorectal cancer were diagnosed worldwide accounting for 9% of cases. In the United Kingdom, 100 new cases are diagnosed each day. In 2005, there were 36766 new cases diagnosed with approximately two thirds in the colon (22748) and one third in rectum (14018) (Cancer Research UK). The distribution of cases in the colon and rectum show that nearly half of all cancers occur in the rectum and left colon (Figure 1.9). In 2006, there were 15975 deaths in the United Kingdom from colorectal cancer (10119 colon, 5838 rectum), making it the second leading cause of cancer death after lung cancer.

The diagnosis of colon cancer is aided by the use of colonoscopy to localise the tumour and obtain histological confirmation of cancer. In addition, colonoscopic examination of the entire colon and rectum is crucial to exclude the presence of

synchronous tumours. Computed tomography is used routinely to screen the chest, abdomen and pelvis for the presence of metastatic disease. Once we have established the absence of disseminated disease and determined the suitability of the patient for surgery with regard to their fitness, surgical resection of the cancer offers the mainstay of primary treatment. Nearly, two thirds of patients will survive 5 years after curative resection, with recurrence being a rare phenomenon beyond four disease free years. Adjuvant chemotherapy is now being offered routinely to patients with high risk disease on histological examination.

Local staging of colonic cancer is gaining increasing importance with the increase in colonoscopic mucosal resection techniques for early tumours. Especially with the introduction of the National Colorectal Cancer Screening programme, detection of colonic cancer may be at an earlier stage with more potential for local treatments. This highlights the importance of accurate local staging of colonic cancer by both colonoscopic and CT techniques. In addition, the possibility of neo-adjuvant chemotherapy being offered to patients with locally advanced cancers also re-iterates the importance of accurate local staging. Screening and neo-adjuvant chemotherapy are discussed briefly prior to examining staging of colonic cancers in detail.

**Figure 1.9 Distribution of colorectal cancers in England 1997-2000
(Cancer Research UK)**



1.2.3.2 Colorectal Cancer Screening

The outcome of patients with colorectal cancer depends on the staging of the disease at the time of presentation. Historically, nearly 90% of symptomatic patients are not diagnosed until deeper penetration of the cancer into the bowel wall with local lymph node metastases (Gill 1978, Umpleby 1984, Stower 1985). The five year survival of patients with Dukes A cancer is favourable at 88% compared to those with advanced stage disease with metastases (7%) (Kievit 1995). It therefore follows that detection of cancer at an early stage is highly curable and this can be achieved by the screening of asymptomatic individuals. The majority of colon cancers arise from adenomatous polyps via the adenoma-carcinoma sequence discussed earlier (Peipins 1994), and removal of these pre-malignant lesions has led to a reduction in colorectal cancer.

Winawer and colleagues (1993) followed a cohort of 1418 patients whom had undergone colonoscopies and removal of one or more adenomata of the colon or rectum. They observed a lower than expected incidence of colorectal cancer in this group of patients followed for a mean of 5.9 years.

There are a number of screening tests that have been employed for the detection of colorectal cancer all of which have been utilised for population based screening.

Faecal Occult Blood Testing

The guaiac smear test is the commonest test used for the detection of faecal occult blood. These are designed to detect blood losses over and above the normal 1.5ml/day of physiological blood loss. The presence of haem releases oxygen from peroxide thereby causing oxygenation of the guaiac chromogen into a blue product which is easily detected. Both rehydrated and dehydrated forms of the test are available with higher sensitivities and lower specificities being achieved with the rehydrated tests (Winawer 1997). Immunochemical tests are also available which utilise monoclonal antibodies against the globin chain of human haemoglobin.

There have been four well designed randomised controlled trials in the United Kingdom (Scholefield 2002), Sweden (Jorgenson 2002), Denmark (Kronborg 2002) and United States (Mandel 1993). All of these have demonstrated a decrease in colorectal cancer mortality by 11-33%. A recent Cochrane Database review (Hewitson 2007) combined the randomised controlled trials in a meta-analysis and showed a significant reduction in mortality of 15-33% (OR 0.85, CI 0.79-0.91). The American Study (Mandel 1993) further showed that mortality was reduced by 33% in the group

which underwent annual screening and this was significantly lower than that of the control group. Importantly, all of the randomised controlled trials (RCTs) demonstrated a favourable shift in disease stage with more Dukes A cancers than Dukes B or C. The FOBTs have commenced as a screening tool in the United Kingdom since April 2000 after the successful pilot studies in Fife, Grampian, Tayside, Coventry and Warwick.

Other tools of screening exist but none of them have been through vigorous RCTs as the FOBT. These include flexible sigmoidoscopy, colonoscopy, computed tomography colonography and molecular markers in stool and serum.

1.2.3.3 Chemotherapy for colon cancer

Adjuvant chemotherapy

The mainstay of adjuvant treatment for colon cancer is fluorouracil, which is a fluorinated pyrimidine that acts through the inhibition of the rate limiting enzyme in pyrimidine nucleotide synthesis, thymidylate synthetase (Sobrero 2000). There is considerable evidence related to adjuvant chemotherapy in colon cancer published over the last 20 years. Prior to 1990 however, there was insufficient evidence to advocate the routine use of chemotherapy in colorectal cancer. Buyse and colleagues (1988) published a meta-analysis of 25 studies and failed to show a significant survival benefit. 17 of these studies specifically examined the role of chemotherapy with control groups with a total of 6791 patients. Fluorouracil containing regimes showed a small benefit in terms of overall survival with an odds ratio of 0.83 in favour of therapy (CI 0.70-0.98). Two hallmark studies in 1989 and 1990 changed the consensus

of chemotherapy in colorectal cancer. Laurie and colleagues (1989) randomised 401 patients with Dukes B and C colorectal cancer to adjuvant chemotherapy (flurouracil alone or in combination with levamisole) and showed that both regimes showed a significant reduction in recurrence with only the combination regime significantly improving overall survival. Levamisole is an anti-helminthic and was examined in combination as an immunomodulating agent. In addition, Moertel et al (1990), from the Mayo clinic, randomised 1296 patients with resected colon cancer either Dukes B or C to adjuvant chemotherapy with flurouracil and levamisole for one year or observation alone. The patients with Dukes C colon cancer could also be randomised to flurouracil alone or in combination with levamisole. They showed conclusively that patients with Dukes C cancer had a 41% reduction in cancer recurrence ($p=0.005$) with an overall reduction of death rate by 33% ($p=0.006$) when treated with the combination regime. Treatment with levamisole alone had no benefit, neither did the results with Dukes B patients draw any definite conclusions. Both of these studies therefore lead to the United States National Institute of Health consensus statements advocating the combination regime in patients with Dukes C colon cancer.

Since the two initial pioneering studies, there have been several studies which have compared flurouracil based regimes against observation with significant improvements in 5 year overall survival in the region of 10%. (Table 1.9) Further queries relating to the length of treatment required, dosage of agent and combination therapy were the subject of several randomised studies. One such study termed the Quick and Simple and Reliable study (QUASAR 2000) recruited 5000 patients and compared high and low dose folinic acid with or without levamisole in addition to flurouracil. Interestingly, no significant differences were seen amongst the groups concluding that

levamisole is not necessary and that low dose folinic acid provided adequate modulation of fluorouracil.

Interestingly, there have been no randomised clinical trials that have demonstrated significant survival benefit for adjuvant chemotherapy in patients with Stage II colon cancer. Gill and colleagues (2004) pooled the results of 7 studies and showed 81% 5 year survival in patients who received fluorouracil regimes compared to 80% in the surgery alone group. Only marginal survival benefits have been shown by the QUASAR study (Gray et al 2004) only published in abstract form, and in subset analyses of the NSABP trials (Mamounas et al 2002). The American Society of Clinical Oncology (ASCO) (Figueredo et al 2004) and the National Comprehensive Cancer Network (NCCN) (Benson et al 2004) have both independently recommended against the routine use of adjuvant chemotherapy in Stage II colon cancer. There are subgroups of patients with Stage II cancer that may benefit from adjuvant chemotherapy and these include those with T4 stage, bowel perforation or bowel obstruction (Moertel 1995).

The discussion of adjuvant chemotherapy has been concentrated to that of fluorouracil as the mainstay treatment regime. However, there is good randomised data from clinical trials advocating the use of other agents such as capecitabine.

(Hoff et al. 2001, Van Cutsem et al. 2001).

Table 1.9 Randomised controlled trials of adjuvant fluorouracil based chemotherapy versus observation alone

Author	No. Patients	5 year survival (%)	
		CHEMOTHERAPY	OBSERVATION
Moertel 1995	929	60	47
Wolmark 1988 (NSABP-C01)	1166	67	60
Francini 1994	239	79	65
IMPACT 1 1995	1526	83	78
O'Connell 1997	309	74	63

NSABP: National Surgical Adjuvant Breast and Bowel Project Protocol C-01 (November 1977 and February 1983)
IMPACT: International Multicentre Pooled Analysis of Colon Cancer Trials

Neo-adjuvant chemotherapy

The past decade has seen neoadjuvant chemotherapy become a routine aspect of oesophageal and rectal carcinomas. The response of the tumour tissue histologically to neoadjuvant chemotherapy and its correlation to clinical outcome has been thoroughly studied (Hiotis et al 2002, Schneider 2005). In contrast, the use of neoadjuvant chemotherapy in the management of advanced nonmetastatic colon cancer is not established in the literature. There are, however, increasing numbers of patients with metastatic colon cancer who are first treated with chemotherapy and later resection of the primary after adequate downstaging. This has identified a group of patients with locally advanced colon cancer who underwent aggressive downstaging after neoadjuvant chemotherapy (Scoggins 1999, Sarela 2001).

Karoui and colleagues (2008) characterised the histological effects of neoadjuvant chemotherapy on primary colonic cancers. 38 patients with Stage IV colon cancer underwent colonic resection either after chemotherapy or without. They demonstrated that chemotherapy induces a major histological regression in 70% of patients and this was comparable to that seen histologically with the liver metastases, and not observed in the control group. Tumour regression grade has been shown to be an important prognostic marker in other gastrointestinal tumours and therefore neoadjuvant chemotherapy may contribute to improved outcome in patients with colon carcinomas. The advantage of other gastrointestinal tumours such as oesophageal and rectal cancers is that clinical tumour and node staging has been evaluated extensively by endoscopic ultrasound, Computed Tomography and Magnetic Resonance Imaging and compared to pathological staging to assess downstaging after chemotherapy (Rodel 2005, Bosset 2005). This has not been the case with colon cancer.

The FOXTROT clinical trial in the United Kingdom (www.foxtrot.bham.ac.uk) has been designed to answer these questions related to the effects of neoadjuvant chemotherapy in patients with locally advanced colon cancer. This is a multicentre randomised controlled trial designed to determine whether neoadjuvant chemotherapy with or without panitumumab, followed by deferred surgery and completion of chemotherapy post operatively, can reduce 2 year recurrence and overall survival as compared to surgery without neoadjuvant chemotherapy. The neoadjuvant chemotherapy would be reserved for locally advanced colon cancers (T3 or T4) without distant metastases and therefore accurate pre-operative staging of colon cancer is a crucial aspect of this study to ensure that patients do not receive unnecessary treatment due to overstaging. Traditionally, Computed Tomography has been the

investigation of choice for local staging and is an integral part of the FOXTROT study. Patients will be selected on the results of the CT examination and poor prognostic indicators will include: T3 tumours with extension beyond 5mm; T4 tumours either involving the peritoneal surface, adjacent organs or perforated tumours (Dighe et al 2008). Therefore all tumours which are T1 or T2 or have evidence of distant metastases will be excluded.

1.2.3.4 Computed Tomography (CT) and local staging of colon cancer

Conventional CT scans have been the investigation of choice in the evaluation of staging of colon cancer. Traditionally, the information available from the images have been limited to the site and size of the tumour, infiltration into surrounding structures and evidence of metastatic spread. The information provided has not been used to change the management of patients with colon cancer except in the light of colonic cancer metastases (Cohen 1992, Thoeni 1995, Isbister 1996). Classically, CT evaluates three major parameters in staging colon cancers: local extramural invasion, regional nodes either greater than 1cm or a cluster of 3 or more nodes each less than one centimetre, evidence of distant metastases and extension of the tumour into adjacent organs (Balthazar 1988). It has been difficult to compare different studies in the literature related to the accuracy of staging of colon cancer as there are great variations in the type of scanners used, the protocols and the methods of administering contrast agents.

Early reports of the evaluation of CT as a staging investigation suggested that the local extent and regional spread of the tumour correlated well with the surgical and histopathological findings. Accuracy rates between 77% and 100% were quoted in the

literature (Dixon 1981, Zaunbauer 1981, Grabbe 1983, Van Waes 1983). However, majority of these studies focused on rectal cancer staging and reliable data of staging proximal to the recto-sigmoid junction is limited.

There are several problems in drawing meaningful conclusions regarding the accuracy of CT in the local staging of colonic cancer. A review of the published literature identified only 20 papers dedicated to local CT staging of colonic cancer, three of which did not include any details regarding staging information, only descriptive terms (Mayes 1980, Meyer 1983, Gossios 1992) leaving only 17 papers for in depth analysis (Table 2). It is therefore not surprising that only a total of 1009 patients have been subject to involvement in a clinical study evaluating the local staging of colon cancer. Seven of the seventeen studies have combined patients with both colon and rectal cancer in their analyses (Thoeni 1981, Thompson 1986, Freeny 1986, Dux 1996, Laghi 2002, Filippone 2004, Kanamoto 2007). The remaining ten studies in the literature, therefore, contribute only 604 patients as the complete number in the published literature on this subject.

Utilisation of contrast in CT

It is well known amongst radiologists that colonic opacification must be optimal, therefore the majority of the studies administered oral contrast either the night before or at least 30-60 minutes before cross sectional imaging. Three studies did not comment on any of the details of the CT scanning protocol (Keeney 1989, Chung 2004, Smith 2007). Of the remaining 14 studies, 2 had no mention of the administration of oral contrast (Hundt 1999, Kanamoto 2007). All of them however, used intravenous contrast during imaging which is encouraging as the potential value

of the use of intravenous contrast to enhance the bowel was relatively recent. Amin and colleagues (Amin 1996, Harvey 1998), described the advantages of intravenous contrast and stated that the potential advantages were not only in providing images of the bowel wall but also of the extracolonic tissues and liver in one setting. This potentially has the benefit of aiding in the assessment of the depth of invasion of colonic cancers, including the identification of pericolic spread, lymph nodes and liver metastases. Contrast enhancement of colonic cancers was evaluated by Hundt and colleagues (1999). They assessed 37 patients with colorectal cancer (23 colonic, 14 rectal) after intravenous contrast and spiral CT and showed that the accuracy of T staging of cancers was 81% in the arterial phase and only 64% in the venous phase, with T1 tumours not being detected in the venous phase. The authors claimed that normal colonic wall can be differentiated into three layers during the arterial phase with the inner layer corresponding to the mucosal layer, the middle low attenuation layer to the submucosal layer and the outer layer corresponding to the muscularis propria and serosa.

Colorectal insufflation/enema

Traditionally, CT has not been the investigation of choice in the evaluation of patients with suspected tumours of the colon. Early and subtle lesions involving the mucosa are difficult to detect, mainly because the colon is not distended (Thoeni 1981). This in addition to poor bowel preparation leaving faecal residue may give erroneous interpretations. Some authors have used water enemas to distend the colon and act as a contrast medium (Gazelle 1995, Dux 1996, Hundt 1999), whereas others have included the administration of rectal insufflation to toleration by the patient (Thoeni 1981, Balthazar 1988, Zerhouni 1996, Filippone 2004, Kanamoto 2007). However, there is

still a wide variation in clinical practice and this is illustrated in Table 2. With respect to water enemas, only 3 authors advocated its use as mentioned earlier, 3 did not mention it in their protocol (Keeney 1989, Chung 2004, Smith 2007) and 11 out of 17 did not use it in their routine practice (Thoeini 1981, Thompson 1986, Freeny 1986, Balthazar 1988, Acunas 1990, Earls 1994, Zerhouni 1996, Laghi 2002, Filippone 2004, Kanamoto 2007, Burton 2008). On the other hand, rectal insufflation was practised by 5 out of 17 institutions, 3 did not mention it in their protocol (Keeney 1989, Chung 2004, Smith 2007) and 9 did not advocate its use (Thompson 1986, Freeny 1986, Acunas 1990, Earls 1994, Gazelle 1995, Dux 1996, Hundt 1999, Laghi 2002, Burton 2008).

Types of CT scanner

Conventional CT imaging in the early 1980s (Thompson 1986, Freeny 1986) relied on staging colon cancer using images acquired at 10mm intervals. Both authors had similar CT protocols with the use of oral and intravenous contrast without rectal enema or insufflation. The accuracies of T staging of colon cancer by these authors vary from 47.5% to 70%. Freeny et al (1986) evaluated 103 patients, 84 of whom had colon cancer using conventional CT at 10mm slices and obtained 47.5% accuracy for T staging with 61.2% sensitivity. They were only able to demonstrate an abnormality suggestive of a tumour in 85% of patients either as a circumferential thickening (34%) or as a discrete mass (66%). In their patients, CT was unable to differentiate between tumour confined to the mucosa or that invading the muscularis propria. Thompson and colleagues demonstrated better accuracies of 70% for T staging in their 25 patients. However, the majority of their patients had rectal cancer (21 out of 25) which may account for this.

The development of CT technology with thinner slice image acquisition and spiral CT with image reconstruction in multiplanar reconfigurations, has led to improving accuracies in the local staging of colon cancer. It seems to be increasingly possible to identify depth of invasion and local nodal involvement. Kanamoto and colleagues (2007) used dual phase contrast enhanced multi-detector row CT at 1mm slice intervals and multiplanar reconstruction, to evaluate local invasion and lymph node metastasis in colorectal cancer. 51 patients were recruited with only 13 rectal cancer patients with an overall T staging accuracy of 94.1%.

T stage

Table 1.10 summarises the 17 studies to date in the literature which have evaluated local staging of colon cancer. This has identified a total of 1009 patients and CT imaging demonstrated a range of accuracies from 43.8% to 96.9%, with sensitivities of 55%-77% and specificities of 57%-80.6%. Eight out of the seventeen studies, however, have included both rectal and colon cancer in their analysis (Thoeni 1981, Thompson 1986, Freeny 1986, Dux 1996, Hundt 1999, Laghi 2002, Filippone 2004, Kanamoto 2007), with two of them not specifying the exact number of colon cancers in their cohort (Dux 1996, Laghi 2002).

Table 1.10: Accuracy of CT staging of colonic cancer

AUTHOR	No. of patients	Slice CT (mm)	T stage (%)			N stage (%)			Liver Mets (%)			Contrast			Water enema	Rectal air	MPR
			Acc	Sen	Spec	Acc	Sen	Spec	Acc	Sen	Spec	Oral	Rectal	IV			
Thoeni 1981	39 (16 colon)	5	92	-	-	-	-	-	-	-	-	√	√	√	X	√	X
Thompson 1986	25 (4 colon)	10	70	77	57	35	22	75	-	-	-	√	√	√	X	X	X
Freeny 1986	103 (84 colon)	10	47.5	61.2	80.6	-	25.9	96	-	72.7	98.9	√	X	√	X	X	X
Balthazar 1988	90	5	58	55	77	68	73	58	93	79	98	√	X	√	X	√	X
Keeney 1989	14	-	57	78	-	-	12	-	-	-	-	-	-	-	-	-	-
Acunas 1990	28	8	71	60	67	75	75	75	93	87	95	√	√	√	X	X	X
Earls 1994	29	10	72	-	-	50	-	-	-	-	-	√	X	√	X	X	X
Gazelle 1995	30	-	76.7	-	-	-	60	79	-	-	-	√	X	√	√	X	X
Zerhouni 1996	237	4	72	68	70	62	56	71	85	62	97	√	X	√	X	√	X
Dux 1996	74 *	-	66	-	-	-	69	46	85	-	-	√	X	√	√	X	X
Hundt 1999	37 (23 colon)	5	81	-	-	81	84.3	60	-	-	-	X	X	√	√	X	X
Laghi 2002	35 *	1	96.9	-	-	-	-	-	-	-	-	√	X	√	X	X	X
Filippone 2004	41(15 colon)	3	83	-	-	80	90	77	-	-	-	√	X	√	X	√	√
Chung 2004	17	-	64.7	-	-	70.6	-	-	-	-	-	-	-	-	-	-	-
Smith 2007	126	-	60.6†	-	-	52.6†	-	-	-	-	-	-	-	-	-	-	-
Kanamoto 2007	51 (38 colon)	1	94.7	-	-	80.5	86.9	79.6	-	-	-	X	X	√	X	√	√
Burton 2008	33	10	43.8†	-	-	59.3†	-	-	-	-	-	√	X	√	X	X	X

The most confusing aspect of colon cancer has been the histological staging of the disease and correlating this with CT staging. The original Dukes system was proposed for rectal cancer was simple and easy to use (Dukes 1938) (Table 1.11). However, this did not classify patients into prognostic groups accurately enough, so Kirklin and colleagues (1949) proposed a modification sub-dividing Stage B into: B1 where there is involvement of the muscularis propria but not through it; and B2 with tumour invasion through the muscularis propria. This sub-division was later extended to Stage C after suggestions from Astler and Collier (1954), with C1 involving nodes in the pericolic region and C2 involving the highest or apical node (Dukes and Bussey 1958). Finally, Turnbull and colleagues added another stage D for the presence of metastatic disease (Turnbull et al 1967).

Table 1.11 Dukes Classification of rectal cancer

Stage	Description
A	Tumour limited to wall of rectum
B	Tumour spread by direct extension through extra-rectal tissues
C	Involvement of regional lymph nodes

There are several variables that affect survival in colorectal cancer and the TNM classification was introduced to bring these together by the International Union Against Cancer (UICC, 1979) and the American Joint Committee for Cancer Staging and End Result Reporting (1978) (Table 1.12)

Table 1.12 TNM classification for staging of colorectal cancer

Stage	Description
Tumour(T)	
Tx	Primary tumour unable to be assessed
T0	No evidence of tumour
Tis	Carcinoma in situ
T1	Tumour invasion into submucosa
T2	Tumour invasion into muscularis propria
T3	Tumour invasion through muscularis propria or non peritonealised pericolic/perirectal tissue
T4	Tumour invades other organs or perforates visceral peritoneum
Lymph nodes(N)	
Nx	Loco-regional nodes cannot be assessed
N0	No lymph node metastases
N1	1-3 pericolic or perirectal lymph nodes involved
N2	≥4 pericolic or perirectal lymph nodes involved
Metastases(M)	
Mx	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases

The published literature varies in the comparisons between histological staging and CT staging. Thoeni and colleagues (1981) correlated their findings to a modified Dukes system and found a high degree of correlation. Zaunbauer et al (1981) used the TNM staging, Van Waels (1983) used Thoeni's modified system, Grabbe (1983) made comparisons with Dukes', and Adalsteinsson (1985) utilised the Astler and Collier modification. Although, this variation exists, these authors concentrated mainly on rectal cancer with no precise data on colon cancer staging. The majority of authors comparing CT and colonic cancer staging have used a TNM based system of classification for interpretation.

The initial studies in the 1980s and early 1990s using conventional CT identified colon cancer as either a discrete mass or focal wall thickening. Thoeni and colleagues (1995) stated that normal colonic wall thickness was less than 3mm, 3-6mm was deemed indeterminate and greater than 6mm was abnormal. They therefore described CT appearances of different stages of tumour. If the cancer was contained within the wall of the colon, the outer margins of the bowel wall appear smooth. Extension of the tumour beyond the colonic wall was visualised as a mass with irregular borders with or without strands of soft tissue extending from the colonic margin to the pericolonic fat. The authors felt that CT was unable to distinguish between the depths of invasion into the different layers of the colon and therefore their results could not be easily compared to the TNM staging as we know it nowadays. Their series could not distinguish between tumours confined to the mucosa and submucosa (T1N0M0) from those invading the muscularis propria but not going through to the serosa (T2N0M0). The high accuracy rates of 92% for T staging of 39 colorectal cancers (16 colonic) was mainly due to the fact that 24 of their patients had advanced disease at either Dukes

Stage C or D. CT frequently understages patients with microinvasion of pericolic fat. This accounts for the low accuracies in T staging shown by both Freeny (1986) and Balthazar (1988). They revealed accuracies of 47.5% and 58% respectively. However, it must be noted that in some of these earlier studies, lymph node metastases were not analysed separately and low sensitivity of detecting lymph nodes (22%, Freeny 1986), lowers overall accuracy of staging.

There have been three studies demonstrating T staging high accuracies above 90%. Thoeni et al (1981), as discussed, had an accuracy of 92% mainly due to the high proportion of advanced cancers. The other 2 studies by Laghi (2002) and Kanamoto (2007) demonstrated T staging accuracies of 96.9% and 94.7% respectively. Both studies adopted 1mm slice image acquisition with multi-detector CT using rectal insufflation and intravenous contrast. Kanamoto and colleagues (2007) showed high accuracy rates for all T1 and T2 tumours combined, T3 and T4 tumours demonstrating accuracy rates of 94.1%, 94.1% and 100% respectively. They used multiplanar reconstruction which they believed was superior to other techniques. Filippone et al (2004) also demonstrated that contrast enhanced multiplanar reconstruction was superior in local staging of cancers. In their cohort of 41 patients (15 colonic cancers), the overall accuracy of T staging was 73% when using the transverse images alone, and this rose to 83% when transverse and multiplanar reconstructed images were used in combination. The authors confirmed increasing accuracy for more advanced cases of colon cancer with 98% accuracy for T4 tumours compared to 93% for T1 and T2 tumour combined. However, all three of the above authors combined both colon and rectal cancers, therefore not giving a true reflection of colonic cancer staging alone.

There are 9 studies in the literature (Table 2) which purely focus on colon cancer staging without inclusion of rectal cancers in their analyses, giving a total of 604 patients with T staging accuracies varying from 43.8% to 76.7% (Balthazar 1988, Keeney 1989, Acunas 1990, Earls 1994, Gazelle 1995, Zerhouni 1996, Chung 2004, Smith 2007, Burton 2008). These CT staging results have been compared to TNM classification without the exclusion of early colonic cancers and without the heavy weighting of advanced cancers in the series, both of which would account for higher accuracy rates in T staging of colonic cancers. Therefore, it may be interpreted that these provide more realistic accuracy rates for T staging of colonic cancers alone.

Recently, it has been argued that T staging of colonic cancers stage may not be important and we should be concentrating our efforts on the identification of colonic cancers that have poor prognosis which may in the future be amenable to neo-adjuvant chemotherapy (Smith 2007, Burton 2008, Dighe 2008). Smith and colleagues reviewed 126 patients with colonic cancer using conventional CT and divided patients into good and bad prognosis groups depending on their T stage. A favourable prognostic group included patients with T1, T2 and early T3 tumours with predicted extramural invasion of up to 5mm beyond the border of muscularis propria. The poor prognostic groups contained advanced T3 tumours with invasion more than 5mm beyond the border of muscularis propria and T4 tumours. The authors showed that 3 year disease free survival was 71% and 43% for CT-predicted good and poor groups respectively, which was similar to the 75% and 43% for histology- predicted good and poor groups. Although their overall T stage accuracy was only 60%, they showed high sensitivity (86-92%) for the identification of T3 and T4 tumours. Burton et al (2008) also showed high accuracies (82% for Radiologist 1, 70% for Radiologist 2) of conventional CT to

predict tumour invasion beyond muscularis propria when compared with histology. Although overall T staging accuracies were low for the 2 radiologists in this series (36% and 51.5%), however this was not as important as the prediction of poor prognostic features known to reduce disease free survival and overall survival in colonic cancers.

Nodal stage

The sensitivities of lymph node prediction by CT vary tremendously in the literature ranging from 22% to 90% (Thompson 1986, Freeny 1986, Balthazar 1988, Keeney 1989, Acunas 1990, Gazelle 1995, Zerhouni 1996, Dux 1996, Hundt 1999, Filippone 2004, Kanamoto 2007). Conventionally, size has been used as a criteria for detecting metastatic lymph nodes. The earlier studies by Thompson (1986) and Freeny (1986) used size greater than 1.5cm as abnormal and showed poor sensitivities for lymph node metastases of 22% and 25.9% respectively. Later, size greater than 1cm was deemed abnormal and Zerhouni and colleagues (1996) showed a sensitivity of 56% in 237 patients with colonic cancer, being the largest colonic cancer staging series to date. In addition to size, abnormality was also detected if a cluster of nodes were seen on CT imaging. The difficulty with using size as the main criteria is that small nodes may harbour metastases and on the other hand, very large nodes may just as well be reactive in nature (Smith 2007).

Lymph node sensitivities obtained using multi-detector CT with contrast enhanced multiplanar reconstruction has been more promising. Filippone et al. showed sensitivity of detection of lymph node metastases of 90% in 41 patients. The authors compared CT findings to TNM classification and diagnosed N1 if a cluster of 3 nodes

were present or if fewer than 3 nodes were present with one being greater than 1cm; N2 if more than 3 nodes were identified; and N3 if enlarged retroperitoneal nodes were present and greater than 1cm. Similarly, Kanamoto (2007) showed sensitivities of 86.9% in 51 patients by evaluating lymph nodes in both the long axis and the short axis diameter and stating that a ratio of 0.8 or greater (short/long axis diameter) was abnormal. Although, both studies show promising results with regard to lymph node staging, both studies combine both colon and rectal cancers with total numbers of colon cancers from both studies totalling only 53 cases (Filippone 2004, n=15; Kanamoto 2007, n=38).

The low sensitivities seen in the published literature (Table 2) with respect to lymph node staging is likely to reflect an inherent inability of CT to detect microscopic involvement as all published series use size as the main criterion and it remains difficult to stray away from this practice. Hundt and colleagues (1999) showed this as 11 out their 34 cases underestimated the N stage due to microscopic involvement of the lymph nodes without enlargement, giving a CT sensitivity of 67.6%.

Summary

The published literature to date is limited with respect to local staging of colonic cancers. Accuracies of T staging in recent series with multidetector CT and contrast enhanced multiplanar reconstruction look promising but future studies focusing purely on colon cancer are needed. With respect to lymph node staging, CT offers poorer sensitivities and specificities when compared to T staging and is not the investigation of choice for accurate detection of local lymph node metastases.

1.2.3.5 Colonoscopic ultrasound

High frequency mini probes have been referred to as catheter probes, high frequency ultrasound (HFUS) and endoscopic ultrasound probes in the literature (Schembre 2005). Whatever their terminology, ultrasound in the colon using probes inserted through the working channel of the standard colonoscope have been shown to have clear advantages over standard endoscopic ultrasound. The probes are easier to use, they may be passed through tight strictures, examine proximal lesions as far as the standard colonoscope can reach during the index colonoscopy and give higher resolution images of the colonic wall (Maruta 1994). This latter fact has led to interest in using HFUS as an adjunct to endoscopic mucosal resection initially in the upper gastrointestinal tract (Takemoto 1992) and more recently in the colon (Hurlstone 2005, 2007).

High frequency ultrasound miniprobe are available in a variety of frequencies (12.5 MHz, 20 MHz, 30 MHz, Olympus, Keymed, Southend-on-sea). The colonic wall visualised with a 12.5 MHz probe has been discussed (Fig 1.7). The wall is seen as a five layered structure alternating between hyperechoic and hypoechoic signals. The first hyperechoic layer is the interface between the water and mucosa. The second hypoechoic layer corresponds to the mucosa. The third hyperechoic is the submucosa, followed by a fourth hypoechoic muscularis propria and the outer hyperechoic serosa. Increasing the frequency to 20MHz scanning offers greater resolution of the colonic wall depicting the muscularis mucosae between the mucosa and the submucosa, and at the same time offering detailed views of the submucosa to define invasion of tumours more precisely.

Evidence from the literature regarding endoscopic ultrasound and staging of colonic cancer is limited. A systematic review was undertaken in order to identify all published studies and identified 24 such publications with a total of 1627 patients (Table 1.13). Twelve of the studies combined data for both colon and rectal tumours (Shimuzu 1990, Cho 1993, Yoshida 1995, Hamada 1998, Tsuruta 1998, Tseng 1999, Norton 1999, Harada 2001, Tseng 2002, Hurlstone 2005, Hurlstone 2007). In addition, 7 studies did not use miniprobe ultrasound to stage colonic cancers and were limited to examine the recto-sigmoid, sigmoid or distal descending colon with a flexible echoendoscope (Shimuzu 1990, Tio 1991, Cho 1993, Kuntz 1997, Tseng 1999, Bhutani 2001, Konishi 2003). Therefore, local staging of colonic cancer or determining depth of invasion using endoscopic ultrasound has been undertaken in only 1406 patients, 991 of whom have had assessment with mini probes alone. Nonetheless, the data clearly demonstrates that T staging of colonic cancer by endoscopic ultrasound is promising across a range of frequencies from 7.5 MHz to 20 MHz, with accuracies ranging from 76-96%. Nodal staging on the other hand is more variable with accuracies ranging from 24.1-90% (Table 1.13).

Table 1.13 : Accuracy of endoscopic ultrasound staging of colonic cancer

AUTHOR	n	Freq / Hz	T stage (%)			N stage (%)			Miniprobe	Acoustic coupling
			Acc	Sen	Spec	Acc	Sen	Spec		
Shimizu 1990	90*	7.5	84.9*	-	-	38.1	-	-	Y	Balloon
Tio 1991	30	7.5	93	-	-	67	91	53	y	Water
Cho 1993	164*	7.5	83*	-	-	-	68	70	N	Balloon
Yoshida 1995	51*	15	76*	-	-	-	-	-	Y	Water
Saitoh 1996	49	20	88	-	-	-	-	-	Y	Water
Kuntz 1997	31	12	85	-	-	90	-	-	N	Balloon
Hamada 1998	33*	15	82*	-	-	87	63	95	Y	-
Tsuruta 1998	45*	20	88.9*	-	-	-	-	-	Y	Water
Tseng 1999	73 (13)*	12	89*	-	-	77	77	76	N	Balloon
Norton 1999	121 (36)*	7.5,12	92*	-	-	65	83	53	Y	-
Hunerbein 2000	49	12.5	92	-	-	85	-	-	Y	Water
Akahoshi 2001	83	12	89	-	-	67	70	64	Y	Water
Bhutani 2001	26	7.5,12	85	-	-	80	-	-	N	Water/Balloon
Harada 2001	35 (22)*	15	85.7*	-	-	-	-	-	Y	Water
Matsumoto 2002	50	12,20	91.8	89.9	90.3	24.1	50	19.2	Y	Water
Tseng 2002	86 (29)*	12	85*	-	-	73	74	71	Y	Water/Balloon
Zhou 2003	96*	12,20	82.7*	-	-	-	55.4	68.8	Y	Water
Stergiou 2003	54	12	94	-	-	84	56	90	Y	Water
Konishi 2003	65	7.5	80,96†	-	-	-	-	-	N	Water
Hunerbein 2004	88	12.5	87	-	-	83	61	94	Y	Water
Hurlstone 2005	130 (102)*	12.5	96*	-	-	87	95	71	Y	Water
Hurlstone 2004	82	20	100% accuracy for detection of sm3 or above						Y	Water/Balloon
Hurlstone 2005 (Gut)	62 (60)	12.5,20	sm1-100%; sm2-92%; sm3-93%						Y	Water/Balloon
Hurlstone 2007	68 (62)*	12,20	sm1-100%; sm2-92%; sm3-92%						Y	Water/Balloon

†Accuracy for villous, non villous tumours

Values in () indicate numbers with colon cancer only; * Values shown for Combined colon and rectal cancers; - missing values not quoted in paper

Acc= Accuracy; Sen= Sensitivity; Spec= Specificity

N= miniprobe not used, flexible echoendoscope instead; Freq=frequency in hertz

T staging

Depth of invasion of early colorectal cancers is important to determine accurately prior to embarking on treatment. Early colonic cancers include those that are confined to the mucosa and submucosa and are thereby classified as T1 on the TNM classification (Greene 2002). Intramucosal cancers have been reported not to harbour lymph node metastases and are therefore easily amenable to endoscopic mucosal resection (EMR) (Morson 1984, Fujimori 2001). On the other hand, cancers invading the submucosa are associated with lymph node metastases depending on the level of invasion. Nascimbeni and colleagues (2002) showed that the risk of lymph node metastases in cancers invading the upper third (sm1), middle third (sm2) and lower third (sm3) were 2%, 9% and 35% respectively. Other series have shown that 6-12% of submucosal cancers have lymph node metastases (Cooper 1983, Kyzer 1992, Minamoto 1993). In any case, the prognosis of patients with colorectal cancer is dependent on the early detection of disease with 95% 5 year survivals achieved in T1 lesions and less than 50% observed in patients with T3 and T4 disease (Berrino 2007). In addition, there is good data from both Japan and the United Kingdom regarding endoscopic mucosal resection and endoscopic submucosal dissection in the management of T1 tumours (Kudo 2000, Hurlstone 2004), re-iterating the importance of accurate local staging of colonic cancer.

Hurlstone and colleagues (2004, 2005, 2007) have consistently shown high accuracy in determining depth of invasion of colonic polyps prior to endoscopic resection using 12.5 and 20 MHz miniprobe ultrasound. In 2004, 82 lateral spreading tumours were subjected to HFUS and magnification chromoscopic colonoscopy, and all 15 of the

tumours invading the muscularis propria (T2 tumour) were accurately identified with 20MHz ultrasound and therefore not subjected to endoscopic mucosal resection. In 2005, the same Sheffield group showed 93% overall accuracy in determining depth of invasion in 62 patients with flat colorectal cancerous polyps using 20 MHz ultrasound. Furthermore, the accuracy for sm1, sm2 and sm3 lesions were 100%, 92% and 93% respectively. Similar accuracies were demonstrated in 2007 by the same group consistently showing the use of HFUS as an aide during endoscopic mucosal or submucosal dissection. High accuracies for depth of invasion for colonic polyps have also been shown using 7.5MHz probes by Konishi and colleagues (2003). They showed accuracies of 80% (12/15) in patients with colonic villous lesions and 96% in non-villous lesions (48/50).

Local T staging of colonic cancers using 12 or 12.5 MHz mini probe ultrasound prior to surgery rather than endoscopic resection has also been undertaken (Hunerbein 2000, Akahoshi 2001, Matsumoto 2002, Stergiou 2003, Hurlstone 2005). Accuracies of T staging varied from 89-96% indicating that depth of invasion can be accurately determined. However, most of the patients in these series had an abundance of T1 and T3 lesions with small numbers of T2 and T4 tumours which may account for the variation in staging accuracies. Tseng and colleagues (2002) used 12 MHz minprobe in 86 patients with colorectal cancer. They showed accuracies for T1, T2, T3 and T4 of 100%, 78%, 93%, 71%. However, only 29 patients had colon cancer and the data reported are that for combined accuracies of colon and rectal cancers. Other groups have also shown varying accuracies for different stages of colonic cancers with a trend of lower accuracies for T2 tumours. Akahoshi et al (2001) showed T staging accuracies of 88% for T1 tumours, 64% for T2, 95% for T3 and 100% for T4 and an

overall accuracy of 89% for all T stages. However, their patient cohort had only one T4 and 11 T2 tumours. Hunerbein and colleagues (2000) stated that they had difficulty in distinguishing T3 and T4 colonic cancers and therefore combined these in their analyses showing T staging accuracies of 91.7% (22/24 tumours). They stated that it was difficult to distinguish penetration into the free peritoneal cavity (T4) from penetration in the mesocolon (T3), as both are associated with complete disruption of the wall layers with irregular outer borders.

Flexible echoendoscopes rather than miniproboscopes have been used with similar accuracies to miniproboscopes. Norton et al (1999), Bhutani et al (2001) and Tio et al (1991) showed T staging accuracies of 92%, 85% and 93% respectively. These authors used 7.5 MHz scopes with water filled balloon plus water infiltration of the colon for acoustic coupling with success. The main reasons why they have fallen out of fashion is that there is a high cost of equipment requiring the use of 2 endoscopes, one for endoscopy and one for ultrasound. In addition, there is difficulty in manoeuvring around tight bends and stenotic tumours increasing the potential risk of perforation.

N staging

There has been ongoing discussion for ultrasound staging of lymph nodes in the gastrointestinal tract as to whether it is possible to detect benign from malignant nodes ever since computer analysis of echo patterns in lymph nodes have shown no difference between benign and malignant nodes (Heintz 1993). However, in the colon, 11 studies have reported on nodal status accuracy ranging from 24.1% to 90% and sensitivities from 50% to 95% (Hamada 1998, Norton 1999, Hunerbein 2000, Akahoshi 2000, Matsumoto 2002, Tseng 2002, Stergiou 2003, Hunerbein 2004,

Hurlstone 2004, 2005 and 2007). The wide variation and some low accuracy in the literature may be explained by the fact that some lymph nodes may be too small to be visible and others may contain micrometastases within inflamed nodes, or some nodes may be out of reach of the miniprobe's range (Hildebrandt 1994). Although there are certain characteristics such as size and hypoechoiccity with well-defined borders suggest malignancy, inflammatory nodes can have a similar appearance (Grimm 1992). Despite this, some groups have shown high sensitivities of nodal staging. Hurlstone and colleagues (2005) demonstrated 87% accuracy and 95% sensitivity in 130 patients with colorectal cancer (102 of who had colon cancer) using 12.5 MHz miniprobe ultrasound. On the other hand, Matsumoto (2002) showed overall nodal staging accuracy of only 24.1% in 50 patients with colonic cancer undergoing 12 and 20 MHz ultrasound.

Summary

Colonoscopic miniprobe ultrasound has been shown to be a useful adjunct to endoscopic mucosal resection providing high accuracies in assessing depth of invasion of colon tumours. There seems to be good data supporting its use in early colonic cancer to assess mucosal and submucosal invasion, with small sample sizes denying us from drawing conclusions in advanced cancers. Nodal staging with mini probe ultrasound is variable and further research needs to be undertaken regarding this. There have no prospective comparative studies of CT staging and miniprobe ultrasound staging of colonic cancer to date.

1.2.4 Malignant polyps

1.2.4.1 Overview

Adenomatous polyps are benign neoplastic epithelium with a potential for transformation to malignancy. Adenomas may be classified into tubular (87%), tubulovillous (8%) and villous (5%) according to the World Health Organisation (WHO) (Castells et al. 2009). Only 5% of adenomas have the potential of malignancy with increasing probability with size greater than 1cm, villous component and in elderly patients (Liu et al 2005).

The numbers of patients with polyps harbouring malignancy is increasing with the introduction of screening programmes for colorectal cancer. The prevalence of colonoscopically removed polyps with malignancy ranges between 0.2% and 11% (Netzer 1998; Volk 1999; Nusko 1997; Soetikno 2008). Often in clinical practice, the presence of a malignant polyp is an incidental and unexpected finding upon review of the histopathology after polypectomy. This may leave both the patient and the clinician in a therapeutic dilemma whether endoscopic treatment is sufficient or whether the patient needs to proceed to radical surgery. Although endoscopic removal is effective in removing polyps even down to the submucosal layer, it carries a risk of residual disease and does not provide assessment of the local lymph nodes. On the other hand, surgery allows both accurate staging and treatment of local and nodal disease, there is a certain morbidity and mortality associated with it especially in patients that are elderly or those who have initial rectal disease. Therefore, patients risk the presence of residual disease after polypectomy or may undergo unnecessary surgery after previous successful polypectomy. In order to reduce such risks for patients and inform them

appropriately, many endoscopic and histological variables have been evaluated to aid in the decision making process. However, official guidelines are still controversial and often cloud the decision making process (Eisen et al 2000).

1.2.4.2 Histological risk factors of malignant polyps

There have been large discrepancies in the terminology used for the diagnosis and evaluation of malignant polyps especially between Japanese and Western pathologists. For this reason, the Vienna Classification was adopted in 1998 offering a common worldwide terminology for gastrointestinal epithelial neoplasia (Table 1.14) (Schlemper et al. 2000).

Table 1.14: Vienna classification of gastrointestinal epithelial neoplasia

Category	Description
1	Negative for neoplasia/dysplasia
2	Indefinite for neoplasia/dysplasia
3	Non-invasive low grade neoplasia (low grade adenoma/dysplasia)
4	Non-invasive high grade neoplasia 4.1 High grade adenoma/dysplasia 4.2 Non-invasive carcinoma (carcinoma in situ)* 4.3 Suspicion of invasive carcinoma
5	Invasive neoplasia 5.1 Intramucosal carcinoma† 5.2 Submucosal carcinoma or beyond

*Non-invasive indicates absence of evident invasion

†Intramucosal indicates invasion into the lamina propria or muscularis mucosae

There are several factors that have been associated with a higher risk of residual disease after polypectomy of malignant polyps or indeed the development of recurrent carcinoma. These include morphology and size of polyp, type of endoscopic resection and margins obtained, stage of differentiation, level of invasion into the polyp, and lymphatic and vascular invasion. Hassan and colleagues (2005) examined 31 studies in the literature with 1900 patients with malignant polyps in order to identify the main histological risk factors and the occurrence of unfavourable outcomes. They concluded that a positive resection margin is predictive of local disease; the presence of poor differentiation associated with a higher cancer related mortality; and the vascular invasion associated with a higher rate of lymph node metastases.

Polyp morphology

Assessment of the polyp prior to the initial resection can alert the endoscopist as to the malignant potential. Sessile polyps have been reported to have a worse clinical outcome when compared to pedunculated lesions with more frequent local disease (9.9% versus 1.4%; Hassan 2005). Other features include size greater than 1 cm, presence of depression or ulceration, irregularity and deformity, a short immobile stalk and the inability to elevate a sessile polyp after submucosal injection. Kudo et al. (1996) described the pit pattern classification for colonic polyps after chromoendoscopy with indigo carmine and magnification colonoscopy (Table 1.15). They clearly demonstrated that the presence of Type 5 pit pattern correlates well with the presence of underlying malignancy.

Table 1.15: Kudo pit pattern classification of colorectal polyps

Pit pattern Type	Characteristics
I	Normal roundish pits (normal mucosa)
II	Stellar or papillary pits (hyperplastic polyps)
IIIs	Tubular or roundish pits smaller than normal (depressed type tumours)
III	Tubular or roundish pits larger than normal (protruded type adenoma)
IV	Sulcus, branch or gyrus-like pits (villous adenoma)
V	Irregular or nonstructured pattern (submucosal or advanced cancers)

Resection type and margin

Endoscopic resection of polyps may be done piecemeal using a snare or en-bloc for smaller polyps or using techniques of endoscopic submucosal dissection (ESD). En bloc removal has been shown to be associated with lower recurrence rates than piecemeal resection. It also enables full histological evaluation of the specimen to evaluate the margins (Church 2003). A recent meta-analysis showed that ESD en bloc resection could be performed in 85% of lesions with clear vertical and lateral margins in 75% of cases (Puli et al. 2009).

The resection margin needs histological evaluation if this is involved or less than 1mm, relapse rates can be as high as 21-33% (Cooper et al. 1995). Resection margins greater than 2 mm is considered safe as the risk of residual disease or recurrent cancer is extremely low (0-2%) (Netzer 1998; Volk 1995; Cooper 1995; Cunningham 1994).

Stage of Differentiation

Prognosis correlates with histological grade with Grade 3 or poorly differentiated carcinomas in polyps having a substantially higher risk of metastatic disease and cancer-related mortality (Hassan et al 2005). Grade 3 differentiation is seen in 5.7% to 9.2% of patients with polyps and the risk of residual disease or relapse is between 36-38% (Cooper 1995).

Level of invasion into polyp

Haggitt and colleagues (1985) suggested that the level of invasion of adenocarcinoma in a polyp is an independent risk factor of an adverse outcome. The authors assigned anatomical levels to each malignant polyp. Level 1 described adenocarcinoma limited to the head of the polyp; Level 2 involving the neck; level 3 the stalk; and level 4 corresponding to the cells infiltrating the submucosa. These levels are more easily applied to pedunculated polyps and by definition invasive carcinoma in a sessile polyp indicated level 4 invasion.

The degree of submucosal invasion can also be classified with sm1, sm2 and sm3 corresponding to the upper, middle and lower thirds of the submucosa respectively. Histologically, sm1 corresponds to depth of invasion being less than 1mm or 1000µm from the muscularis mucosae (Paris classification 2002; Kikuchi et al 1995). The risk

of lymph node metastases increases substantially from 1-3%, 8% to 23% as you progress from sm1 to sm2 to sm3 respectively (Tytherleigh et al 2002). The Japanese have studied submucosal invasive in considerable detail and Kitajima and colleagues (2004) clarified the relationship between submucosal depth and the rate of lymph node metastases. Interestingly, they showed that in pedunculated polyps with submucosal invasion, the rate of lymph node metastases was 0% if the head was involved and also 0% when the stalk was invaded less than 3mm or 3000 μ m. For these pedunculated polyps, Haggitt level 2 was used as the baseline for making measurements. Additionally, for non pedunculated polyps, the rate of lymph node metastases was also 0% if the submucosal invasion was less than 1mm or 1000 μ m.

Lymphatic invasion

Lymphatic channels are usually present within the superficial submucosa and the muscularis mucosae with rare extensions into the lamina propria or mucosa. This near absence of lymphatics within the mucosa suggests that patients with intramucosal carcinoma do not have the potential for lymph node metastases. However, this view has been challenged with some studies have shown that there is proliferation of lymphatics in the stalk and mucosa of adenomas and early invasive cancers (Fogt et al 2004; Walgenbach et al 2006). These authors used the antibody D2-40 which stains lymphatic endothelium to demonstrate this. Interestingly, there are no recognised guidelines for establishing the presence of lymphatic invasion with considerable inter and intra observer variability in the interpretation of samples. This often leads to diagnostic difficulties and most pathologists end up using a more cautious approach (Cooper et al 1998).

1.2.4.3 Imaging modalities

We have seen that unfavourable histology is when the resection margin is less than 2mm; there is piecemeal resection, in poorly differentiated carcinomas with lymphatic and vascular invasion. These histological parameters are often discussed after polypectomy with an incidental finding of carcinoma within the polyp, in order to provide the patient with an informed view prior to deciding whether to continue endoscopic surveillance or embark on surgical resection. For endoscopic surveillance in favourable circumstances, follow up colonoscopy is often carried out at 3 months after polypectomy and also at 1 year, 3 and 5 years (Alabi et al 2009).

Endoscopic ultrasound is widely used to stage rectal tumours pre-operatively to aid decision making regarding local resection or radical surgery. There is limited data in the literature with only 2 studies investigating the use of this imaging modality to detect residual disease and local lymphadenopathy after polypectomy with an incidental finding of adenocarcinoma. Both of these studies examine rectal polyps with no data on endoscopic ultrasound in the colon (Kruskal 1999; Garcia-Aguilar 2005).

Kruskal and colleagues (1999) performed endorectal ultrasound in 18 patients whom had undergone polypectomy and found to have an incidental carcinoma, prior to surgical resection. They found that ultrasound was able to detect residual tumour after polypectomy with a sensitivity of 100%, specificity of 44%, positive predictive value of 64% and negative predictive value of 100%. However, in this small series, the precise T stage of the tumour was correctly predicted in only 44% of cases. In their series, they overstaged 7 cases and five of these did not show evidence of residual tumour after surgical resection. In each case, the ultrasonographic abnormality was

hypoechoic and the authors were not confident in distinguishing this from residual tumour with their 7-10 MHz mechanical endoprobe.

Garcia-Aguilar and colleagues (2005) also used utilised endorectal ultrasound (ERUS) in the management of patients with malignant rectal polyps. They followed 63 patients whom had undergone endoscopic polypectomy for malignant polyps with ERUS, either 7 or 10 MHz probe. The ERUS images at the polypectomy site were defined as normal when the 5 layer pattern was preserved, as cautery artefact when the layers were expanded but echoic characteristics of the different layers were preserved. Any hypoechoic image at the polypectomy site was defined as residual tumour. In their series, the accuracy of assessing the presence of residual tumour was 90 per cent. However, the negative predictive value was only 86 per cent indicating that a normal ultrasound does not exclude the possibility of residual tumour in the surgical specimen.

1.3 Diverticular disease

1.3.1 Pathophysiology

Diverticula were first reported in the early 18th century by Littre and were originally thought not to cause any clinical symptoms, but were rather viewed as pathological curiosities (Finney et al. 1928). It wasn't until 1849, when Cruvehiler described small herniations of the mucosa through the muscle layer of the sigmoid colon (Cruvehiler 1849). Diverticular disease relates to the presence of diverticula in the colon and this may affect over half of the population in the United Kingdom over the age of 65. There has been an increased prevalence of diverticular disease, particularly in industrialised nations since the 20th century. Although it is rare under the age of 30, more than 40% of individuals develop diverticulosis by the age of 60 and over 60% by the age of 80 years or older (Almy et al. 1980; Jacobs et al. 2007). Diverticula tend to involve the sigmoid and left colon in more than 95% of cases in Western society with increasing right sided diverticula in elderly and Asian populations (Hughes 1969; Sugihara et al. 1984).

Colonic diverticula are pulsion or false diverticula containing only mucosa and muscularis mucosa and not all layers of the bowel wall. They appear macroscopically as saccular outpouchings acquired as a result of persistently raised intra-luminal pressures with penetration of the diverticula through areas of weakness of the circular muscular layer. This tends to be the point where the vasa recta penetrate the circular muscle layer with herniation's therefore occurring at well-defined points around the

circumference of the colon along either side of the mesenteric taenia and on the mesenteric border of the 2 antimesenteric taenia (Slack 1962).

The pathophysiology of the development of diverticular disease has resulted from a combination of disordered motility and generation of high intracolonic pressures (a process termed segmentation); role of dietary fibre and structural abnormalities of the colonic wall termed “elastosis”. Segmentation refers to the process of high intracolonic pressures being generated within individual colonic segments especially within the sigmoid colon which then probably leads to mucosal herniation and the development of diverticulosis (Painter et al. 1965). The early studies of diverticular disease compared populations of Africa and the United Kingdom and concluded that the higher incidence of diverticular disease in the UK was due to the lower quantities of fibre consumed. Indeed, Painter and Burkitt studied colonic transit times and stool weights in more than 1000 patients and discovered longer transit times and lower stool weights in the UK population as compared to their African counterparts (Painter and Burkitt 1971).

Alternative theories to the low fibre hypothesis are related to colonic wall abnormalities. Early post mortem studies revealed an increased thickness of bowel wall in patients with diverticular disease (Slack 1962). This was initially thought to be due to muscle hypertrophy and hyperplasia but this was discounted by Whiteway and colleagues (1985) who proposed that the thickening was actually due to the elastin deposition within the taenia. The authors examined the muscularis propria in patients with diverticular disease and discovered that the taenia were thickened with greater than 200% increase of elastin in these patients as compared to controls. Furthermore,

the elastin deposition in a contracted form leading to bunching of the taenia and therefore shortening of the bowel. Therefore, in diverticular disease, the circular muscle which controls peristalsis becomes thicker and the longitudinal muscle condensing in taenia coli is shorter pulling the colon to a relatively short length. Interestingly, Wess and colleagues (1995) added that patients with diverticular disease have an abnormally high degree of collagen cross-linkage in the colonic wall which causes the tissues to become stiffer and less resistant to stretching. This subsequent loss of compliance of the colonic submucosa makes it more susceptible to tears when subject to segmentation and could therefore potentially lead to segmentation.

The descriptions above show that the diverticula are the result of the secondary effect of the primary muscle abnormality, and therefore it seems likely that patients show a pre-diverticular phase of the disease. However, the majority of these patients are asymptomatic and therefore do not come to the attention of clinicians (Ming et al. 1998; Silen 1995). Pathologists regularly recognise this muscular thickening on resected colonic specimens for other pathologies without the presence of diverticula (Ming 1998). Radiological studies have also shown that such pre-diverticular disease is the precursor of classic diverticular disease with formation of diverticula after several years (Feischner et al 1964).

1.3.2 Imaging modalities

Incidental asymptomatic diverticulosis is commonly seen on radiological imaging studies. However, diagnostic imaging specifically performed for diverticular disease is

essentially limited to imaging of suspected acute diverticulitis and complicated diverticular disease.

With regard to diverticulitis, plain film radiography is of little value and classical contrast enemas have been superseded by Computed Tomography with sensitivity rates of 80-92% and 99% respectively (Baker et al. 2008; Balthazar et al. 1990). Transabdominal ultrasound has also been shown to have sensitivities ranging from 77-98% for diagnosis of diverticulitis, but is operator dependent and is not as accurate as CT for identifying alternative diagnoses (Lameris et al. 2008; Pradel et al. 1997; Schwerk et al. 1992). Magnetic resonance imaging (MRI) is comparable to CT in diagnosis and offers the advantage of no radiation exposure, but is seriously limited by the inability to drain intra-abdominal abscesses (Heverhagen et al. 2008; Ajaj et al. 2005).

Endoscopic assessment of diverticular disease is simply for assessment of the entire colon to exclude other diagnoses and confirm the diagnosis including absence or presence of colitis. There is no grading system in place for severity of disease and endoscopic assessment is purely of the mucosa rather than evaluation of the underlying layers of the bowel wall. Colonoscopic ultrasound using high frequency mini probes have been described earlier in the assessment of colorectal cancers and polyps. However, there is no data in the literature regarding assessment of the colonic wall in diverticular disease. In fact, there is limited data on mini probe ultrasound utilisation in benign disease. The normal colorectal wall can clearly be visualised as stated in previous chapters. This is as a five layered structure: the first corresponding to the echo of the overlying mucosa; second corresponds to the mucosa; third layer to the

submucosa; the fourth to the muscularis propria; and the fifth layer to the border echo of the serosa. Tsuga and colleagues (1998) used mini probe ultrasound to measure the colorectal wall thickness in ulcerative colitis and compared thickness with normal controls. They concluded that transmural assessment of the colorectal wall used in conjunction with clinical and endoscopic parameters may contribute to the diagnosis and treatment of ulcerative colitis.

The utilisation of high frequency mini probe ultrasound for assessment of diverticular colonic wall thickness may provide additional diagnostic information in symptomatic diverticular disease which may prove useful especially in patients in the pre-diverticular phase. The feasibility of such a technique is subject to investigation in this thesis.

CHAPTER 2

Aims and Experimental Design

CHAPTER 2

2.1 BACKGROUND

2.1.1 Colonic cancer

Colorectal cancer is the third commonest cancer worldwide after lung and breast cancer with over two thirds of cancers occurring in developed nations. In excess of one million new cases of colorectal cancer are diagnosed worldwide annually with almost 40,000 new cases diagnosed in the UK (approximately two thirds in the colon and one third in rectum) (Cancer Research UK).

The high incidence and substantial mortality of colorectal cancer have led to major developments in early detection and its treatment. With increased patient and clinician awareness of the diagnosis and a national colorectal cancer screening program in the UK, the proportion of patients with early colonic cancer may increase substantially. The most important prognostic factor is the stage of disease and it now apparent that local staging of the disease may play a major role in determining whether neo-adjuvant chemotherapy prior to surgery is indicated. There are a number of ways to stage the disease, each of which has their advantages and disadvantages and these have been outlined in the introduction.

Local staging of colonic cancer has traditionally been evaluated by Computed Tomography (CT) but the information provided with CT has not transformed the management of colon cancer except in the case of distant cancer metastases. CT imaging has demonstrated a range of accuracies from 43.8% to 96.9%, with sensitivities of 55%-77% and specificities of 57%-80.6% for tumour (T) staging. The sensitivities of lymph node involvement predicted by CT vary tremendously in the literature ranging from 22% to 90% (Acunas 1990; Zerhouni 1996; Chung 2004). The main drawback with CT imaging is that it cannot differentiate between the different layers of the colonic wall. It is therefore problematic to differentiate between T1 and T2 tumours.

There has been increasing interest to stage colonic cancers using endoscopic ultrasound in a similar fashion as staging rectal cancers. However, it has not been technically feasible to stage tumours in the proximal colon via this modality due to bulky flexible endoscopes with ultrasound attachments. The introduction of mini probe ultrasound through the working channel of the colonoscope has made lesions in the proximal colon more accessible but evidence of superiority over current staging techniques from the literature is limited.

2.1.2 Rectal tumours referred for Transanal Endoscopic Microscopic Surgery (TEMS)

TEMS is indicated in certain patients with biopsy proven benign tubulovillous adenomas. However, surgical histopathology reveals post excision carcinoma is 21-34% of such cases (Doornebosch 2008; Galanduick 1987; Taylor 1981). EUS may raise suspicion of malignancy in the presence of benign biopsies. There is some evidence that previous TEMS procedures may increase the morbidity of subsequent radical surgery (Baron 1995, Friel 2002, Hahnloser 2005). Therefore it is vital that accurate pre-operative staging is available for all patients undergoing local excision with TEMS.

Traditional endorectal ultrasound offers accurate assessment of the depth of invasion in early rectal tumours with an overall accuracy of 87% and a sensitivity and specificity of 93% and 78%, respectively. This compares with MRI which offers 82%, 86% and 77% corresponding values (Kwok 2000). Rigid transrectal ultrasound (7.5-12 MHz), however, is not feasible in all patients due to tumours being further proximal to the dentate line and stenosis. Ultrasound examination with mini probes would overcome these problems but there are limited studies address this in the literature.

2.1.3 Malignant colorectal polyps

Patients who have undergone snare polypectomy for malignant polyps are a management challenge. The decisions regarding further surgery or endoscopic surveillance are a balance between the assessments of risk of residual disease or involved local lymph nodes against the morbidity and mortality of surgical resection.

Malignant polyps confined to the mucosa are not thought to pose a risk of lymphatic or haematogenous spread due to the absence of lymphatics within the mucosal layer (Fenoglio 1973). However, increased risk of lymph node metastasis is proportional to the depth of invasion into the submucosa (Kikuchi 1995).

Endorectal ultrasound has been utilised for risk assessment post polypectomy of malignant rectal polyps in relation to residual disease and local lymphadenopathy (Garcia-Aguilar 2005). The assessment of malignant polyps in the proximal colon using high frequency mini probes inserted through the working channel of the standard colonoscope is now possible (Maruta 1994).

2.1.4 Diverticular disease

Diverticular disease is an increasingly common benign disease of the colon, which causes significant morbidity and mortality.

The colon in diverticular disease appears shortened with a thickened muscular wall, redundant mucosal folds, and diverticula disposed in two to four parallel longitudinal rows between the mesenteric and the antimesenteric teniae. The longitudinal and circular muscle in the teniae appears thickened (Whiteway and Morson 1985; M J Ford 1995). The assessment of colonic wall thickness may be assessed by CT when patients are admitted with complications of diverticular disease such as diverticulitis. However, assessment of colonic wall thickness in symptomatic diverticular disease patients has not been undertaken routinely but has now become feasible with the development of colonoscopic high frequency mini probes.

2.2 HYPOTHESIS AND AIMS

The central aim of this thesis was to investigate the feasibility of endoscopic high frequency mini probe ultrasound in the assessment of colorectal disease. This role was colonoscopic ultrasound was specific to 4 areas examined in this thesis:

1. Investigate the role of colonoscopic high frequency ultrasound in the local staging of colonic cancers and compare this prospectively with the local staging undertaken by Computed Tomography (CT).
2. Investigate the role of colonoscopic high frequency ultrasound in the assessment of rectal tumours referred for TEMS and in particular assess the depth of infiltration of rectal polyps in comparison to Magnetic Resonance Imaging.
3. Investigate the role of colonoscopic high frequency mini probe ultrasound in the examination of the colon and rectum after excision of malignant polyps to assess for residual disease and local lymphadenopathy
4. Investigate the feasibility of colonoscopic high frequency ultrasound in the assessment of diverticular disease and compare the thickness of colonic wall of symptomatic diverticular patients with normal subjects.

To address each individual aim, the following experimental series was undertaken.

2.3 EXPERIMENTAL DESIGN

Approval was sought from the Kings College Hospital Committee on the Ethics of Human Research prior to the recruitment of patients. Potential subjects were approached and written informed consent obtained.

To address the first aim of the thesis, patients scheduled for elective surgery for curative resection of colonic cancer were approached and recruited after informed consent. All patients underwent CT of the abdomen and pelvis and colonoscopic high frequency ultrasound of the colonic tumour. A prospective comparison of the local staging of colonic cancer between CT and ultrasound was undertaken, and compared to the gold standard of post-operative histology.

The second aim of the thesis was addressed by recruiting patients referred for TEMS. All patients underwent MRI of the pelvis for local staging of the tumour and in particular for evaluation of the depth of invasion of the rectal polyp. This was compared with the colonoscopic ultrasound findings for depth of invasion and compared to the gold standard of histopathology.

To address the third aim, patients discovered to have a focus of incidental adenocarcinoma after endoscopic resection, were recruited after informed consent. These patients were evaluated with colonoscopic high frequency ultrasound to identify any residual disease or the presence of local lymphadenopathy, and followed up closely for detection of recurrent disease.

Finally, symptomatic diverticular disease patients who were due to have colonoscopy were recruited. Colonoscopic high frequency ultrasound was used to measure the thickness of colonic wall in the mid sigmoid colon and this compared to thickness of colonic wall at a similar site in normal colons.

CHAPTER 3

Materials and Methods

CHAPTER 3

3.1 PROJECT SET-UP

3.1.1 Ethical Approval

The first step was to gain approval for the study from the King's College Hospital Committees on the Ethics of Human Research. This study began in 2008, after the introduction of the standardised Centralised Office for Research Ethics Committees (COREC) forms, which are now used nationwide for all applications to conduct research involving humans. The relevant local application form was completed, along with the submission of a Patient Information Sheet and Patient Consent Form. This application was considered by the King's College Hospital Committees on the Ethics of Human Research and following some minor amendments to the Patient Information Sheet, ethical approval was granted. Four separate ethics applications were submitted for each of the four sub studies considered in this thesis.

The summaries of the protocols and patient information leaflets, consent forms and letters to General Practitioners are outlined in Appendix 1. A summary of the proposed study protocols for each of the studies, along with the patient inclusion and exclusion factors are shown in Figures 3.1-3.4.

Figure 3.1: Prospective comparison of Colonoscopic high frequency mini probe ultrasound and conventional Computed Tomography (CT) in the local staging of colonic cancers

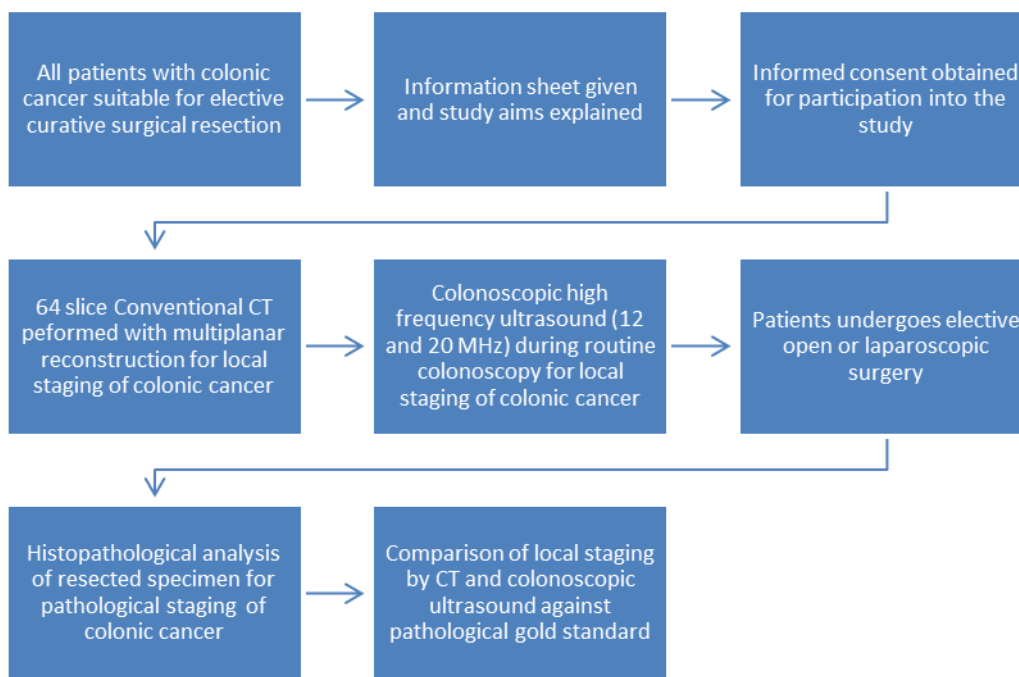


Figure 3.2: High frequency mini probe ultrasound in the assessment of rectal tumours deemed suitable for Transanal Endoscopic Microsurgery (TEMs) – A comparison with Magnetic Resonance Imaging (MRI).

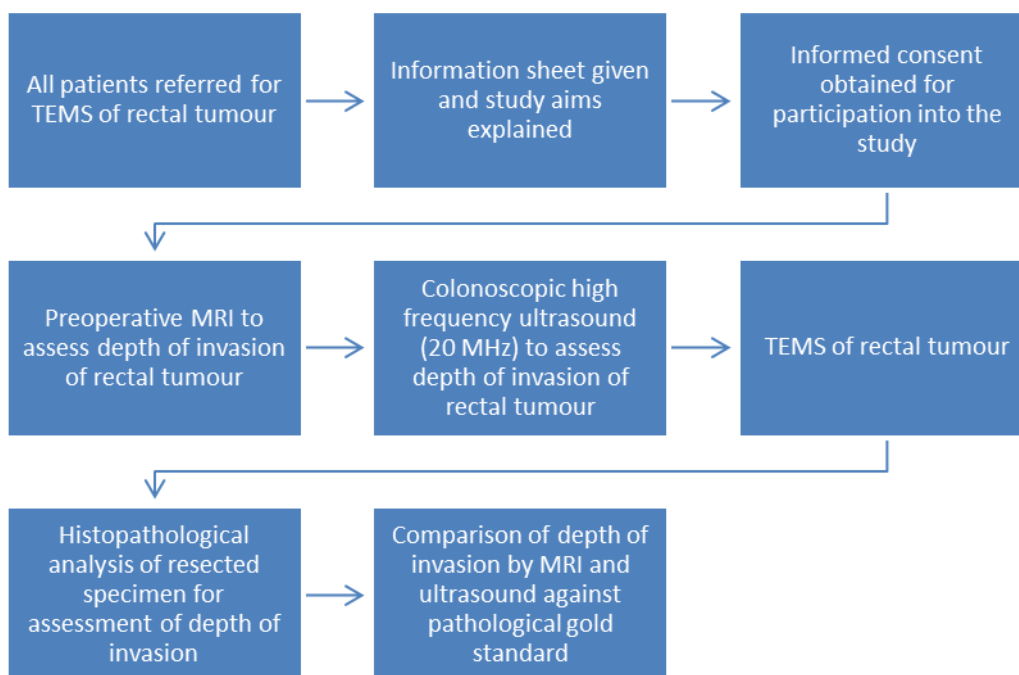


Figure 3.3: High frequency mini probe ultrasound as a useful adjunct in the management of patients with malignant colorectal polyps.

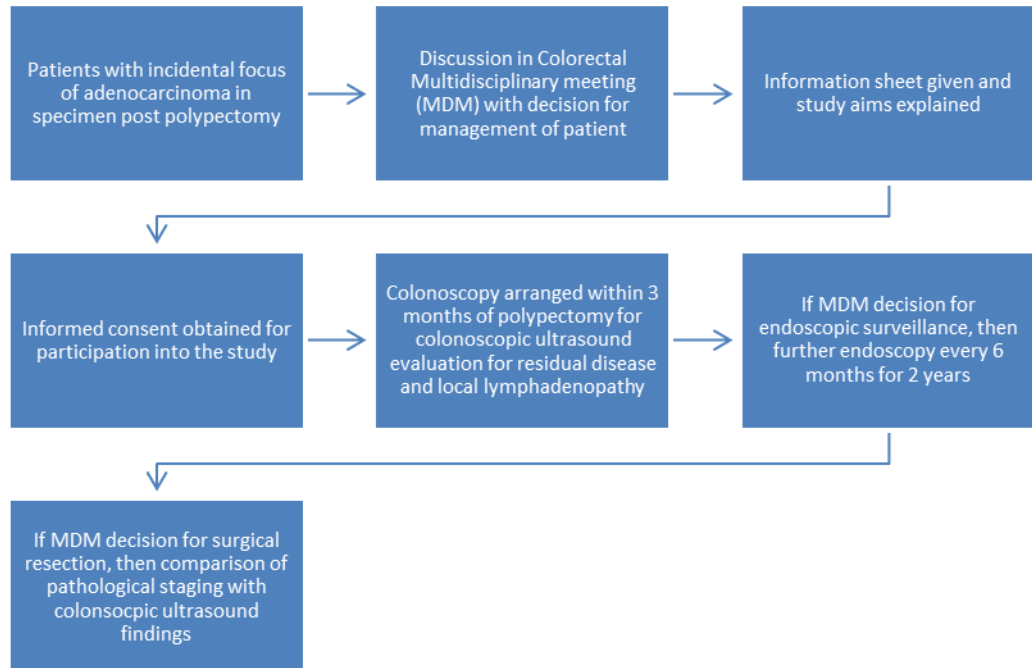
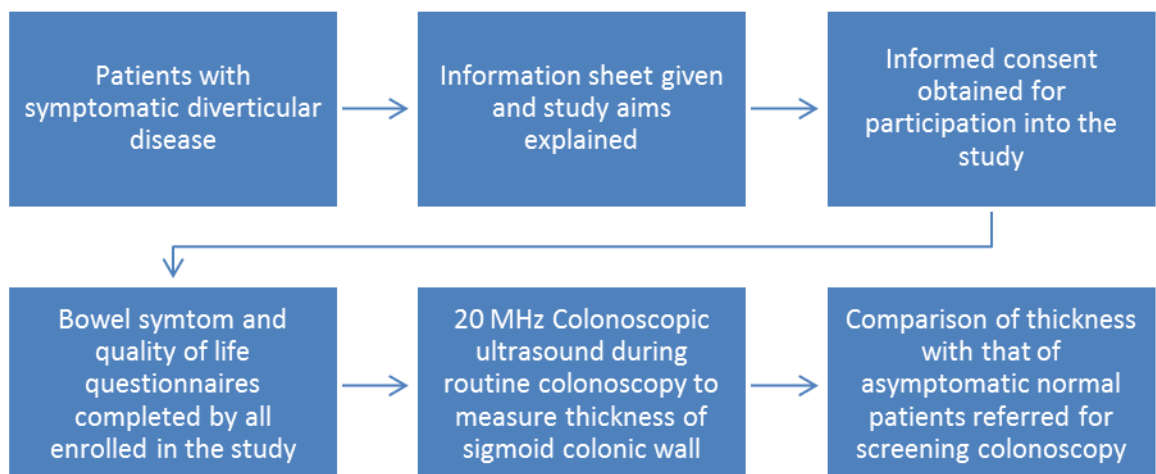


Figure 3.4: Utilisation of high frequency mini-probe ultrasound in the assessment of colonic wall thickness in patients with diverticular disease



3.1.2 Research and Development Approval

Before patients could start being recruited for the study, approval was sought from the local Research and Development Committee at King's College Hospital NHS Trust. This process also entailed ensuring that the study met the demands of the Data Protection Act (1998), with respect to the plans made for storing patient information; all data was kept on a password-protected computer database, within a double locked office. Furthermore a coding system was employed, making it impossible to link experimental results with patient identifiers.

3.1.3 Patient Recruitment

Potential eligible study subjects were identified with the help of the colorectal cancer nurse specialist and the committee members of the Colorectal Multidisciplinary Team (MDT), and approached either as an outpatient or whilst an in-patient on the ward, prior to surgery. Following a clear and thorough explanation to both the patient, and any relatives present, regarding the nature, aims and demands of the study, an information sheet was offered and a short period of time left for deliberation. If the patient was willing to participate in the study, then any final queries were addressed, and they were asked to complete and sign a consent form. There were some special circumstances for each of the individual sub studies and these are addressed individually

3.1.3.1 Colonic tumours

Prospective comparison of Colonoscopic high frequency mini probe ultrasound and conventional Computed Tomography (CT) in the local staging of colonic cancers

The patients diagnosed with colorectal cancer in the hospital are all discussed in the Colorectal Multidisciplinary Meeting (MDM) prior to any treatment or management decisions. Therefore, recruitment of patients was primarily from the MDM or with assistance from the Colorectal Nurse Specialists. Patients with rectal cancer were

excluded from the study as were patients not eligible for curative surgical resection. This was defined as tumours within 15 cm from the anal verge or below the peritoneal reflection on CT and MRI. Therefore, any tumours offered neo-adjuvant radiotherapy fitted into this category. Some patients were recruited directly from endoscopy or from the outpatient clinic and consented prior to their colonoscopy explaining to patients that they would only be recruited into the study if a colonic cancer was discovered. In this manner, unnecessary additional colonoscopic examinations were avoided.

3.1.3.2 Rectal tumours

High frequency mini probe ultrasound in the assessment of rectal tumours deemed suitable for Transanal Endoscopic Microsurgery (TEMS)

King's College Hospital offers a tertiary referral service for TEMS. All patients are referred to one Consultant Surgeon and these patients are all discussed in the Colorectal MDM. Recruitment was via this meeting and patients were approached in the Colorectal Outpatient department or in the Endoscopy Unit prior to their routine flexible sigmoidoscopy.

3.1.3.3 Malignant polyps

High frequency mini probe ultrasound as a useful adjunct in the management of patients with malignant colorectal polyps.

The recruitment was via the Colorectal MDM with assistance from the Colorectal Nurse Specialists, and patients were consented in the Colorectal Outpatient department.

3.1.3.4 Diverticular Disease

Utilisation of high frequency mini-probe ultrasound in the assessment of colonic wall thickness in patients with diverticular disease.

Within the trust, all patients with diverticular disease are referred to a specialist outpatient clinic with support from a Specialist Nurse dedicated to this disease. Asymptomatic patients who had incidental diverticular disease on routine colonoscopy were excluded. Symptomatic patients were approached in the Diverticular Disease Clinic. Normal subjects without diverticular disease, on the other hand, were identified from the Endoscopy Unit. Only patients with no lower gastrointestinal symptoms were included and these were either patients within the colorectal cancer screening program or asymptomatic patients with previous colorectal polyps undergoing colonoscopy during routine follow up.

3.2 Endoscopic ultrasound

3.2.1 Equipment

The colonoscopic ultrasound scans undertaken within our unit for the purposes of this thesis were undertaken by the author using both 12 and 20 MHz catheter mini probes (UM-2R and UM-3R Olympus, Japan) inserted through standard colonoscopes used for routine endoscopy. The miniprobe connected to a drive unit and processor attached to a television monitor to display radial ultrasound images. All of the images were captured using plain Sony photographic paper and stored for further analyses if necessary.

Acoustic coupling for ultrasound imaging was achieved by the use of a water jet pump delivered through the “ERBE diathermy” machine and water delivered through the working channel of the colonoscope upon depression of a foot pedal. In addition, water can also be delivered through the working channel of colonoscopes using standard 50 ml syringes.

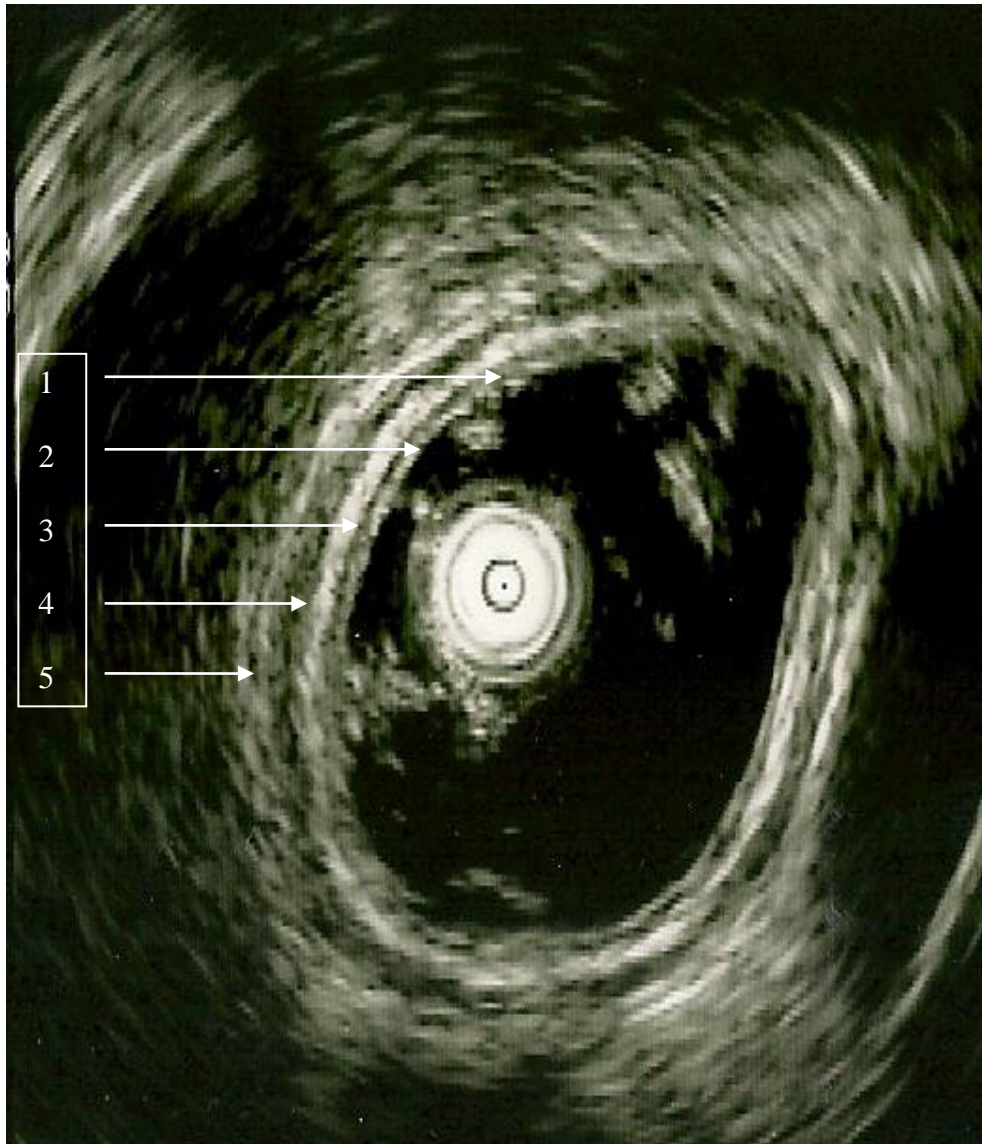
3.2.2 Technique

Patients were recruited into the study after informed written consent for research and also for colonoscopic examination of their bowel. Patients received sedation and analgesia for colonoscopy as per the department protocol which advocates the use of 2mg midazolam and 25 micrograms of Fentanyl routinely. Patients were placed in the left lateral position to start with and moved to supine or right lateral positions if necessary during the examination. The colonoscope was inserted in the standard

fashion to examine the entire length of colon. Once the pathology was encountered, adequate lavage of the area was undertaken to ensure that no faeculent material was present as this would obscure and create artefact for ultrasound imaging. Excessive air was suctioned from the bowel to prevent air artefact for ultrasound and air insufflation was reduced to a minimum or even switched off if views were adequate. Water was instilled via the working channel of the colonoscope to completely submerge the area in question, tilting the patient or changing their position to allow gravity to aid this process. The mini probes were then introduced through the working channel of the colonoscope after lubrication with aquagel and the probe advanced until the ultrasound probe could be seen to lie adjacent to the pathology. Ultrasound imaging was conducted with the probe completely submerged in water and approximately 0.5-1cm from the pathology. The whole area was imaged sequentially and representative images captured on photographic paper. The colon was then suctioned to drain the excess water and air insufflation re-started in order to withdraw the colonoscope safely from the bowel.

Ultrasound imaging using 12 MHz mini probe ultrasound produces a 5 layered image of the colorectal wall (Figure 3.5). This is seen as a series of concentric rings of differing echogenicity. The first 2 layers are hypoechoic which corresponds to the mucosa and muscularis mucosae. The 12 MHz ultrasound does not differentiate between these 2 layers as they are both hypoechoic. The third layer is hyperechoic and is the submucosa. The echoic layers alternate as you traverse through the gut wall thereby demonstrating the fourth layer as hypoechoic (muscularis propria) and the fifth serosal layer as hyperechoic.

Figure 3.5 The layers of the gut wall on radial 12 MHz endoscopic ultrasound



1-Interface between water/balloon and colonic wall

2-Mucosa/Muscularis mucosae

3-Submucosa

4-Muscularis Propria

5-Serosa

The ultrasound examinations were carried out by the author and although other medical personnel were present during the examinations, the final image interpretation of the pathology in question was conducted by the author himself. Therefore there was no inter-observer variability that needed to be taken into account. The author was familiar with endorectal ultrasound and had performed over than 100 procedures prior to undertaken colonoscopic mini probe examination and therefore it was felt that the learning curve for the procedure was short. Initially, there were some technical difficulties with achieving acoustic coupling. It was noted that if air insufflation was used during colonoscopy then it was imperative to terminate the air insufflation once the pathology was encountered, excess air suctioned and then the colon irrigated with normal saline (0.9%) completely so that the pathology was submerged with fluid. Patients needed to be moved into various positions including left and right lateral, supine and prone, head up and head down in order for gravity to assist with the pathology being submerged in fluid prior to ultrasound examination. Bowel preparation should also be optimal as any faecal residue particles would create an artifact for the ultrasound.

The depth of invasion of colorectal tumours were carefully evaluated by the mini probe ultrasound by ensuring sequential imaging of the entire surface of the tumour under direct endoscopic examination. In this manner, the tumour was identified as hypoechoic in nature traversing through the layers of the colorectum and this was assigned a tumour (T) stage.

Examination for local lymphadenopathy was undertaken with the same protocol for every case. Sequentially scanning in a radial fashion was undertaken after acoustic

coupling was achieved 10cm above and below the tumour in question using both frequencies of miniprobcs. This identified lymph nodes of any size as well defined hypoechoic oval or round lesions with the 5 cm focal length of the ultrasound probes. It was not possible to identify the exact anatomical location of the nodes and these were either pericolic or mesenteric nodes.

The thicknesses of the colonic wall measurements were undertaken using the higher frequency probe. The mini probes need to be placed perpendicular to the colonic wall being evaluated otherwise this would give false readings. This is described in more detail in Chapter 7.

3.3 STATISTICAL ANALYSIS

Statistical analyses were conducted after importing data from Microsoft Excel 2007 and analysed using Graphpad Prism version 5 and STATA (v9). All results were summarised using descriptive statistics. Normally distributed data was presented as mean values with s.e.m. (in parenthesis).

Weighted Kappa coefficients were calculated to assess the accuracy of each imaging modality against the pathological assessment (gold standard). Ordinal logistic regression models were used to compare the imaging modalities while assessing other factors that may have influenced accuracy (i.e. age, gender and location). The sensitivity, specificity, positive predictive value, negative predictive value, accuracy and kappa coefficients of each imaging modality were also calculated against the histopathological gold standard.

CHAPTER 4

Endoscopic Ultrasound and Colonic Cancer

CHAPTER 4

4.1 INTRODUCTION

Colorectal cancer is the third commonest cancer worldwide after lung and breast cancer with over two thirds of cancers occurring in developed nations. In the United Kingdom, 100 new cases are diagnosed on average each day, with a third being localised to the rectum and two thirds more proximally in the colon.

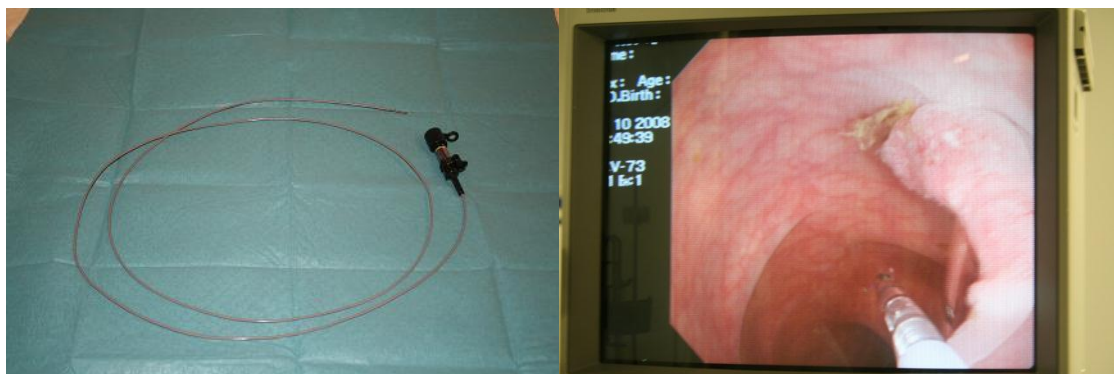
Accurate local staging of colonic cancer is increasingly important. Increased awareness of the diagnosis and a national colorectal cancer screening program may increase the detection rates of early colonic cancer with increased potential for local treatment. The possibility of neo-adjuvant chemotherapy prior to surgery is dependent on accurate local staging, which historically has been assessed by CT.

Computed Tomography (CT) is presently the investigation of choice in the evaluation of staging of colon cancer. This technique aims to provide assessment of the site and size of the tumour, infiltration into surrounding structures and metastatic spread. At present, neo-adjuvant therapy is offered to patients with demonstrable metastatic disease on the staging CT scan (Cohen 1992; Isbister 1996; Thoeni 1995). Current evidence based CT guidelines recommend assessing for local extramural invasion as a sign of T3, regional nodes either greater than 1cm or a cluster of 3 or more nodes (each less than one centimetre) as a sign of involvement, and distant metastases and / or extension of the tumour into adjacent organs as a sign of T4 disease (Balthazar 1988). Recently, there has more interest in the evaluation of CT for local staging of colon cancer (Burton 2008; Smith 2007) especially in the detection of locally advanced tumours as these may be a group amenable for neo-adjuvant chemotherapy and there is an on-going national randomized trial on the potential role of neo-adjuvant chemotherapy in advanced colonic cancer (www.foxtrot.bham.ac.uk).

Ultrasound in the colon using high frequency mini probes inserted through the working channel of the standard colonoscope is of particular interest because of its ease of use, its ability to assess lesions proximal to the rectum (outside the range of conventional

endoscopic ultrasound) and with the advent of higher frequency probes, its potentially increased sensitivity in predicting mural invasion due to high resolution images (Maruta 1994) (Figures 4.1).

Figure 4.1: High frequency mini probe ultrasound (Olympus Keymed, Southend-on-Sea)



To date, there are no studies comparing local staging of colonic cancers by modern CT with high frequency mini probe ultrasound. We compared conventional CT and high frequency mini probe ultrasound in the local staging of colonic cancer in relation to the histopathological findings.

4.2 METHODS

Consecutive patients listed for surgical resection for colon cancer from March 2008 and November 2009 were entered into the study after informed written consent. All patients underwent diagnostic colonoscopy and biopsy for histological confirmation of malignancy. In addition, both 12 and 20 MHz (Olympus Keymed UM-3R, Japan) mini probe high frequency ultrasound was performed in a back to back design either during the index colonoscopy or on table during general anaesthesia prior to laparoscopic or open colonic resection. If colonoscopy was undertaken in the operating theatre, insufflation was always using carbon dioxide as this is readily absorbed and would not cause untoward colonic distention making laparoscopic surgery hazardous.

Acoustic coupling was achieved during colonoscopic ultrasonography by suctioning of excess air and water instillation in the colon to submerge the tumour completely. The patient's position was changed frequently to allow gravity to aid in submerging the tumour completely with water without the presence of large air bubbles. Water was instilled either by the use of a syringe through the working channel of the colonoscope or the utilisation of water pump with continuous irrigation of fluid through the working channel controlled by a foot pedal. The entire tumour was sequentially scanned under endoscopic vision and the depth of invasion recorded as the Tumour (T) stage of the hyperechoic lesion traversing the layers of the colonic wall. Local lymphadenopathy was noted as well defined hypoechoic lesions either in the pericolic or mesenteric distribution. The colon was submerged with fluid in order allow sequential scanning 10 cm above and below the tumour.

Images were captured on Sony photographic paper and also real time ultrasound recorded onto super VHS format to enable further review if necessary. Two authors were present during ultrasound examination. However, the main author was responsible for staging the colonic cancer alone and only he was blind to the results of the CT local staging. As 2 authors did not independently stage the cancers, inter-observer variability was not explored. The time taken to perform the colonoscopic ultrasound was recorded both for 12 and 20 MHz examinations. This was defined as the time between initial insertion of the mini probe through the working channel and

the time of withdrawal from the same channel at the end of the procedure. The main author was responsible to collect all the data.

All patients underwent 64 slice CT of the chest/abdomen and pelvis using intravenous and oral contrast with multiplanar reconstruction (MPR) using 2 millimetres slices. No bowel preparation was administered pre procedure and the colon was not distended. All patients were scanned after a 70 second delay in the portal venous phase. 100mls of iohexol was injected at a rate of 2-3ml/sec. Images were evaluated by an experienced colorectal radiologist with 13 years of abdominal radiology experience. All images were evaluated in axial images alone, and then axial combined with MPR reformat. Lesions were classified as T1 or T2, if no tumour was demonstrated to breach the muscularis propria; T3, if the tumour demonstrated a nodular pushing edge that breached the muscularis propria; and T4, if the tumour was demonstrated to directly involve adjacent organs.

Nodal metastases or positivity on CT was defined as either a single node greater than 1 cm or a cluster of 3 nodes each greater than 3 mm. With respect to high frequency ultrasound, size was not a criterion and well defined hypoechoic nodes were taken as positive.

The local staging of colonic cancers by the two imaging modalities were compared to the standard histological T (tumour) and N (nodal) stage after colonic resection. Histological analysis was conducted in a standardised protocol by a single experienced Colorectal Pathologist as per guidelines issued by the Royal College of Pathologists in order to collect the minimum dataset.

Statistics

Weighted Kappa coefficients were calculated to assess the accuracy of each imaging modality against the pathological assessment (gold standard). This comparison was done using weighted kappa coefficients where weights of 0.7 to 0.8 were given to

penalize disagreements of one level in either direction and weights of zero were given to penalize disagreements of more than one level in any direction.

Ordinal logistic regression models were used to compare the three imaging modalities while assessing other factors that may have influenced accuracy (i.e. age, gender and location). The sensitivity, specificity, positive predictive value, negative predictive value of nodal involvement was also calculated.

All data was collected prospectively onto Microsoft Excel and the statistical packages STATA (v9) and Graphpad Prism 5 were used for all calculations.

4.3 RESULTS

38 patients were recruited into the study after informed written consent. Of these, 22 patients (58%) were female. The mean age was 65 (SD 13.2, range 38-89). Location of colonic cancers were sigmoid (n=20), caecum (n=7), descending (n=5), ascending colon (n=2), splenic flexure (n=2), transverse colon (n=1) and hepatic flexure (n=1) (Table 4.1). All patients underwent surgical resection, 21 undergoing laparoscopic surgery and 17 open colorectal resections.

Table 4.1: Location of colon cancers evaluated by colonoscopic ultrasound and CT

Location of tumour in colon	Number of cases	Mean distance from anal verge (cm) <i>range in parentheses</i>	Proportion of total (%)
Sigmoid	20	18.25 (15-40)	52.6
Descending	5	51 (45-65)	13.2
Splenic flexure	2	72.5 (70-75)	5.3
Transverse colon	1	50	2.6
Hepatic flexure	1	70	2.6
Ascending colon	2	77 (74-80)	5.3
Caecum	7	87 (76-95)	18.4
Total	38		100

Acoustic coupling was achieved in all 38 patients (100%) using 12 MHz ultrasound and in 34/38 patients (89%) using 20 MHz ultrasound. The reasons for the failure included artefact secondary to excess air in the colon (n=2) and failure to completely submerge in the tumour with water despite position changes of the patients (n=2). Mean procedural time for 12 and 20 MHz scanning was 8.5 (SD 3.4, range 5-22) and 7.7 (SD 2.2, range 5-15) minutes respectively. This was in addition to the time taken for routine colonoscopy. CT was able to visualise the tumour in all cases both in axial and reformatted multiplanar images.

T stage

Histopathological examination of the resection specimen revealed 7 T1, 4 T2, 25 T3 and 2 T4 cancers.

Table 4.2: Observed histological T stages of colonic cancer

T stage	Number of cases	Proportion of total (%)
T1	7	18.4
T2	4	10.5
T3	25	65.8
T4	2	5.3
Total	38	100

Overall, imaging agreement with histology was observed in 82% (31/38) and 82% (28/34) using ultrasound at 12 MHz or 20 MHz ultrasound respectively, while for CT was only observed in 42% (16/38) of the patients. Some of the observed agreement may have been due to chance alone. Hence, agreement of measure was evaluated in terms of the weighted Kappa coefficients for the 4 level diagnostic tests (Table 4.9). These are calculated by first measuring the percentage of agreement between any two diagnostic methods and then adjusting these values, discounting the amount of agreement that could be expected due to chance alone. The weights take into account the ordered nature of the classification and the fact that a misclassification by one level is less severe than one by two or more levels. The p-values reported test the null hypothesis that the Kappa coefficient is zero.

In relation to the histopathological results (Tables 4.3-4.4 and Figures 4.4, 4.5a & 3b, 4.6a-4c), CT

- ◆ Incorrectly classified all the 7 T1-tumours, overstaging 6 as T2 and 1 as T3.
- ◆ Correctly classified only one of the 4 T2-tumours, under-staging 1 as T1 and over-staging 2 as T3.

- ◆ Correctly classified 15 of the 25 T3 tumours, under-staging 7 as T2 and over-staging 1 as T4 and 2 as T1. This yields a sensitivity of 60% and specificity of 62% for this classification.
- ◆ Incorrectly classified the 2 T4 tumours under-staging them both as T3.

The weighted Kappa coefficient for CT in relation to the gold standard, histopathology, was 0.36 (SE=0.14).

Table 4.3: Agreement between CT and histopathology for T staging of colonic cancers

	cT1	cT2	cT3	cT4	Total
pT1	0	6	1	0	7
pT2	1	1	2	0	4
pT3	2	7	15	1	25
pT4	0	0	2	0	2
Total	3	14	20	1	38

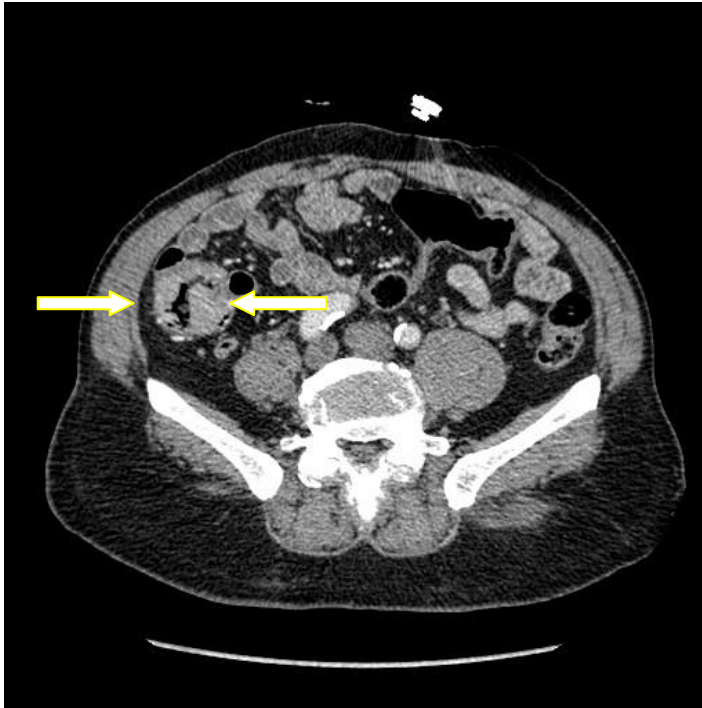
p=pathological staging
c=CT staging

Table 4.4: Overall accuracies of CT for individual T stages of colonic cancer

	Sensitivity	Specificity	PPV	NPV
T1	0 (0-0.41)	0.90 (0.74-0.98)	0(0-0.71)	0.80 (0.63-0.92)
T2	0.25 (0.01-0.81)	0.62(0.44-0.78)	0.07 (0-0.34)	0.88 (0.68-0.97)
T3	0.60 (0.39-0.79)	0.62 (0.32-0.86)	0.75 (0.51-0.91)	0.44 (0.22-0.69)
T4	0 (0-0.84)	0.97 (0.85-0.99)	0 (0-0.98)	0.95 (0.81-0.99)

95% confidence intervals in (parentheses)
PPV=positive predictive value
NPV=negative predictive value

Figure 4.2: Histopathological T1 stage caecal carcinoma

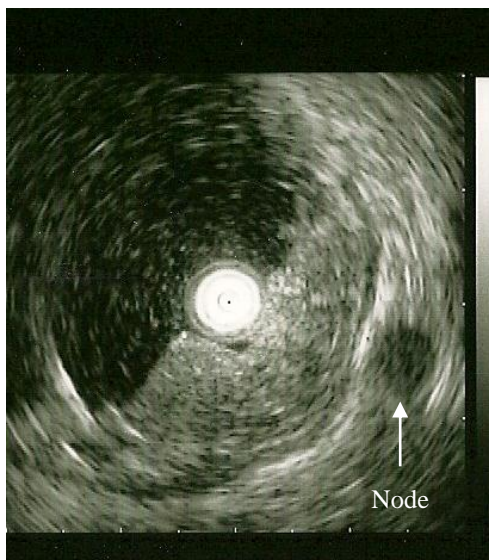


CT was unable to differentiate colonic wall layers overstaging this T1 lesion as T2

Figure 4.3: Histologically staged T3N1 descending colon cancer

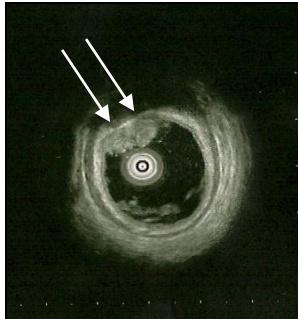


(a) CT correctly staged as T3

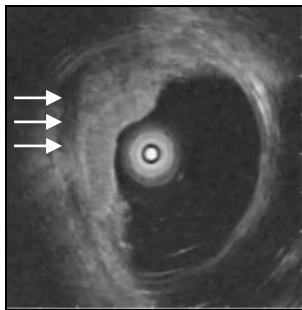


(b) 12 MHz ultrasound correctly staged as T3N1

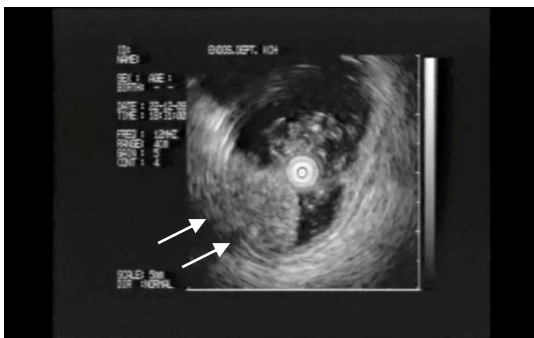
Figure 4.4: 12 MHz ultrasound images of local staging of colonic cancers



T1 tumour infiltrating the submucosa but not extending to muscularis propria (arrows)



T2 tumour abutting the muscularis propria (arrows) but not extending through this layer



T3 tumour infiltrating through the muscularis propria (arrows)

In relation to the histopathological results (Tables 4.5-4.6), 12 MHz ultrasound,

- ◆ correctly classified 5 of the 7 T1-tumours, over-staging two: 1 as T2 and one as T3;
- ◆ correctly classified 2 of the 4 T2-tumours;
- ◆ Correctly classified 24 of the 25 T3-tumours, under-staging 1 as T2. This offered 96% sensitivity and 69% specificity;
- ◆ incorrectly classified the 2 T4-tumours, under-staging them both as T3.

The weighted Kappa coefficient for ultrasound 12 MHz in relation to the gold standard was 0.81 (SE=0.17).

Table 4.5: Agreement between 12 MHz mini probe ultrasound and histopathology for T staging of colonic cancers

	uT1	uT2	uT3	uT4	Total
pT1	5	1	1	0	7
pT2	1	2	1	0	4
pT3	0	1	24	0	25
pT4	0	0	2	0	2
Total	6	4	28	0	38

p=pathological staging
u=ultrasound staging

Table 4.6: Overall accuracies of 12 MHz mini probe ultrasound for individual T stages of colonic cancer

	Sensitivity	Specificity	PPV	NPV
T1	0.71(0.29-0.96)	0.97(0.83-0.99)	0.83(0.36-0.99)	0.94(0.79-0.99)
T2	0.50(0.07-0.93)	0.94(0.80-0.99)	0.5(0.07-0.93)	0.94(0.80-0.99)
T3	0.96(0.80-0.99)	0.69(0.39-0.91)	0.86(0.67-0.96)	0.90(0.56-0.99)
T4	-	-	-	-

95% confidence intervals in (parentheses)

PPV=positive predictive value

NPV=negative predictive value

In relation to the histopathological results (Tables 4.7-4.8), 20 MHz ultrasound:

- ◆ correctly classified 4 of the 6 T1-tumours, over-staging two: 1 as T2 and 1 as T3;
- ◆ correctly classified 2 of the 4 T2-tumours;
- ◆ correctly classified all of the 22 T3-tumours. This offered 100% sensitivity and 67% specificity;
- ◆ incorrectly classified the 2 T4-tumours, under-staging them both as T3.

The weighted Kappa coefficient for ultrasound 20 MHz in relation to the gold standard was 0.81 (SE=0.17).

Table 4.7: Agreement between 20 MHz mini probe ultrasound and histopathology for T staging of colonic cancers

	uT1	uT2	uT3	uT4	Total
pT1	4	1	1	0	6
pT2	1	2	1	0	4
pT3	0	0	22	0	22
pT4	0	0	2	0	2
Total	5	3	26	0	34

p=pathological staging; u=ultrasound staging

Table 4.8: Overall accuracies of 20 MHz mini probe ultrasound for individual T stages of colonic cancer

	Sensitivity	Specificity	PPV	NPV
T1	0.67(0.22-0.96)	0.96(0.82-0.99)	0.80(0.28-0.99)	0.93(0.77-0.99)
T2	0.5(0.07-0.93)	0.96(0.72-0.99)	0.67(0.07-0.93)	0.92(0.72-0.99)
T3	1.0(0.85-1.0)	0.67(0.35-0.90)	0.85(0.65-0.99)	1.0(0.63-1.0)
T4	-	-	-	-

95% confidence intervals in (parentheses)

PPV=positive predictive value

NPV=negative predictive value

On a multivariate ordinal logistic regression, CT and both ultrasounds at 12 and 20 MHz showed a highly significant association with the pathology classification while age ($P=0.89$), gender ($P=0.71$) and location (sigmoid versus other $P=0.25$) were not significant either as a main effect or in interaction with any of the diagnostic methods ($P=0.80$). The odds of a higher level in the pathology result were significantly higher for higher level classification in the ultrasound 12 MHz and 20 MHz ($P<0.001$)

- ◆ 15-fold higher for CT=T1-T2 in relation to CT=T3-T4 ($P=0.002$).
- ◆ 81-fold higher for US-12 MHz=T3 in relation to US-12 MHz=T1-T2 ($P<0.001$)
- ◆ 94-fold higher for US-20 MHz=T3 in relation to US-20 MHz=T1-T2 ($P=0.001$)

Table 4.9: Weighted Kappa coefficients for T stage agreement with the histopathology gold standard.

	Agreement %	Expected agreement %	Kappa	Standard error	Z	P value
CT	81.0	71.1	0.36	0.14	2.6	0.01
12 MHz	94.2	69.6	0.81	0.16	5.1	<0.0001
20 MHz	94.4	70.6	0.81	0.17	4.9	<0.0001

N stage

Histopathological examination demonstrated 15 out of 38 patients to be node positive with respect to metastases (39.5%). CT offered 80% sensitivity and 48% specificity for detection of node positive disease with an overall accuracy of 61%. 20 MHz ultrasound offered an overall accuracy of 65% with 23% sensitivity and 90% specificity. However, 12 MHz ultrasound was significantly better than both CT and 20 MHz with 80% sensitivity, 83% specificity and an overall accuracy of 82% ($p < 0.001$) (Tables 4.10-4.13).

Table 4.10: Agreement between CT and histopathology for nodal status in colonic cancer

	CT node positive	CT node negative	Total
Histology node positive	12	3	15
Histology node negative	12	11	23
Total	24	14	38

Table 4.11: Agreement between 12 MHz ultrasound and histopathology for nodal status in colonic cancer

	12 MHz node positive	12 MHz node negative	Total
Histology node positive	12	3	15
Histology node negative	4	19	23
Total	16	22	38

Table 4.12: Agreement between 20 MHz ultrasound and histopathology for nodal status in colonic cancer

	20 MHz node positive	20 MHz node negative	Total
Histology node positive	3	10	13
Histology node negative	2	19	21
Total	5	29	34

Table 4.13: Overall accuracies of CT, 12 and 20 MHz ultrasound for assessment of nodal status in colonic cancer

	Accuracy %	Sensitivity	Specificity	PPV	NPV	Kappa (SE)
CT	61	0.80 (0.52-0.96)	0.48 (0.27-0.69)	0.50 (0.29-0.69)	0.79 (0.49-0.95)	0.25 (0.14)
12 MHz	82	0.80 (0.52-0.96)	0.83 (0.61-0.95)	0.75 (0.48-0.93)	0.86 (0.65-0.97)	0.62 (0.16)
20 MHz	65	0.23 (0.05-0.54)	0.90 (0.70-0.99)	0.60 (0.15-0.95)	0.66 (0.46-0.82)	0.15 (0.13)

SE=standard error

4.4 DISCUSSION

This initial pilot feasibility study demonstrates that high frequency mini probe ultrasound out performs CT for local staging of colorectal cancer. CT scan is currently used primarily for staging distal metastases of solid organs but its value in local staging of colonic tumours is yet unproven. The 12 and 20 MHz mini-probe ultrasound did not differ in their overall accuracies of staging both offering 82% accuracy. The paucity of T2 (n=4) and T4 (n=2) tumours may influence these results and further patients need to be evaluated in order to draw firm conclusions in the assessment of these T stages. The largest group of 25 patients with T3 tumours were accurately staged with both 12 and 20 MHz offering sensitivities of 96% and 100% respectively, with good agreement showing high kappa values at 0.81 for both frequencies of ultrasound. This contrasts with conventional CT which demonstrated significantly less sensitivity (60%) and specificity (62%) for this group.

Evidence from the literature regarding endoscopic mini probe ultrasound and staging of colonic cancer is limited (Akahoshi 2001; Hunerbein 2000; Hurlstone 2005; Matsumoto 2002; Stergiou 2003). Nonetheless, our accuracy for T staging of 82% for 12 MHz US is similar to that quoted which vary from 89-96% using 12 or 12.5 MHz US. Most of the patients in the published series have an abundance of T1 and T3 lesions with small numbers of T2 and T4 tumours, as was in our material. Tseng and colleagues (2002) used 12 MHz miniprobe in 86 patients with colorectal cancer. They showed accuracies for T1, T2, T3 and T4 of 100%, 78%, 93% and 71%, respectively. However, only 29 patients had colon as opposed to rectal cancer. Other groups have also shown varying accuracies for different stages of colonic cancers with a trend of lower accuracies for T2 tumours. For instance Akahoshi et al (2001) showed T staging accuracies of 88% for T1 tumours, 64% for T2, 95% for T3 and 100% for T4 and an overall accuracy of 89% for all T stages. However, their patient cohort had only one T4 and 11 T2 tumours.

Our CT accuracy of 42% is difficult to compare with previous studies as there are great variations in the type of scanners used, the protocols and the methods of administering contrast agents. Early reports of the evaluation of CT as a staging investigation suggested that the local extent and regional spread of the tumour correlated well with the surgical and histopathological findings. Accuracy rates between 77% and 100% were widely quoted (Dixon 1981; Grabbe 1983; van Waes 1983; Zaunbauer 1981). However, majority of these studies focused on rectal cancer staging and data of staging of proximal lesions are limited. In addition, all of the studies with increased overall sensitivity define T4 as direct organ invasion only, and not peritoneal fat invasion, which falsely increase the accuracy rates. This does not apply to our findings but in part explains their higher rates.

Laghi et al (2002) and Kanamoto et al (2007) demonstrated T staging accuracies of 97% and 95%, respectively. Both studies adopted 1mm slices image acquisition with multi-detector CT using rectal insufflation and intravenous contrast. Combining T1 and T2 tumours and T3 and T4 tumours suggested accuracy of 94% and 100%, respectively (Kanamoto 2007). This study used multiplanar reconstruction which they believed was superior to other techniques. This is contrary to our findings and also to the findings of other authors. It should be stated that we did not use bowel preparation or rectal insufflation for obtaining CT images and this may account for our low accuracy of 42%. Combining T1 and T2 tumours as one group and T3 and T4 tumours as another gave CT a slightly better accuracy of 68% (26/38 correctly identified) in the T staging of colonic cancers, but still not comparable to that achieved by Laghi (2002) and Kanamoto (2007). Some of the apparent discrepancies in the literature may be due to the failure to separate rectal from colonic cancers (Balthazar 1988; Burton 2008; Smith 2007; Acunas 1990; Chung 2004; Earls 1994; Gazelle 1995; Keeney 1989; Zerhouni 1996).

Dighe and colleagues (2010) summarized the literature regarding local staging of colonic cancer by CT in a recent metanalysis of 19 studies. The sensitivity and specificity for differentiating between T1/T2 and T3/T4 tumours was reported as 86% and 78% respectively. In a subgroup analysis they showed that the best results were

obtained in studies that used axial slices of 5 mm or less and those that used rectal insufflation with air or water during imaging. Furthermore, it is interesting to note that the 13 studies which used spiral or multidetector CT had better pooled sensitivity and specificity of 93% and 81% respectively. With regard to nodal status, the pooled analysis showed a sensitivity of 70% and specificity of 78% with once again best results being obtained using multidetector CT.

In our series, the relative small number of node positive patients tempers the interpretation of results. Never the less, 12 MHz US (which has a higher tissue penetration than the higher frequency probe) was significantly superior with overall accuracy of 82% compared to 61% and 65% offered by CT and 20 MHz US, respectively. 11 studies have reported on nodal status accuracy for colonic cancer ranging from 24% to 90% and sensitivities from 50% to 95% (Akahoshi 2000/2001; Hunerbein 2000; Hurlstone 2005; Matsumoto 2002; Stergiou 2003; Tseng 2002; Hamada 1998; Hurlstone 2005; Norton 1999). Hurlstone and colleagues (2005) demonstrated 87% accuracy and 95% sensitivity in 130 patients with colorectal cancer (102 of who had colon cancer) using 12.5 MHz miniprobe ultrasound. The wide variation and some low accuracies in the literature are almost certainly due to the fact that histological micrometastases are impossible to differentiate from inflamed nodes, and indeed some nodes may be out of reach of the miniprobe's range (Hildebrandt 1986). The latter is thought to be the reason for lower accuracies seen with the higher frequency 20 MHz probe.

Lymph node staging using our mini probe technique will always have one crucial flaw. Some may argue that the method of examining for lymphadenopathy is somewhat arbitrary as the whole length of the colon 10 cm above and below the tumour is sequentially scanned. This is likely to under stage the extent of disease as the focal length of the probes is no more than 5 cm and therefore it is unlikely to identify nodes further away from the tumour which are crucial to the nodal staging of the patient. Furthermore, with our technique it is impossible to be certain that the "abnormal" lymph node identified on ultrasound is the identical abnormal lymph node isolated on histopathological specimen. It is also not possible on ultrasound to be accurate in

identifying the anatomical region of the lymphadenopathy such as pericolic or mesenteric.

The initial review of the literature with respect to both T and N staging of colonic cancers have shown great variability of the results which are in part due to the technical nature of the staging technique with a learning curve. In this study, the main author was trained in endorectal ultrasound using the rigid probe and utilized his knowledge of staging rectal cancers to that using mini probes for staging of colonic cancers with the assumption that as he was trained and over the learning curve in transrectal ultrasound, and that this would be similar for colonoscopic mini probe examinations. There is some evidence of the existence of a learning curve in transrectal ultrasound but the literature is poor with respect mini probe ultrasound. Carmody et al (2000) compared local staging of rectal cancer in 36 patients performed by a single surgeon who was inexperienced in performing the procedures. The accuracy of staging improved over the study period with a 58.5% accuracy in the initial 12 examinations to 87.5% accuracy in the remaining 24 patients. Orrom et al (1990) also showed a steady improvement in rectal cancer staging accuracy over a 31 month period with improvements from 58% to 95% from a single surgeon. Interesting Li et al (2010) did not show any improvement with respect to T stage but marked change with nodal staging. They reported on 50 patients whom underwent transrectal ultrasound over a 2 year period. The overall accuracy for T staging was 86% and this did not change significantly from the early period (84%) to the later group (88%). On the other hand, accuracy for lymph node staging improved in the same time period from 52% to 80% with overall N staging of 66%. The authors stated that experience was particularly important for nodal staging and felt that the learning curve was overcome between 25-40 cases. For the purposes of my study, it was assumed that experience with previous transrectal ultrasound was transferable to colonoscopic ultrasound and this is largely true as the colonic images are very similar. However, this may have affected the results of nodal staging and it would be interest to evaluate this further with larger numbers in the study. Interestingly, Siridawana et al (2009) felt that colonoscopic ultrasound was still associated with a learning phenomenon despite experience with a transrectal rigid probe with poor sensitivity of colonic ultrasound at 61% in local staging of 44 rectal cancer patients. However, they used a colonoscopic

ultrasound 7.5 MHz flexible echoendoscope for the purposes of their study. Although there is no data regarding learning curve for mini probe ultrasound, my personal experience suggests that once the technical aspects of the acoustic coupling are overcome, image interpretation skills are transferable from the transrectal ultrasound experience.

The reported sensitivities of lymph node prediction by CT vary substantially ranging from 22% to 90% (Balthazar 1988; Kanamoto 2007; Acunas 1990; Gazelle 1995; Keeney 1989; Zerhouni 1996; Dux 1996; Filippone 2004; Freeny 1986; Hundt 1999; Thompson 1986). Our sensitivity of 80% for CT at the expense of low specificity of 48% and poor agreement with kappa coefficient of only 0.31 is in keeping with previous studies. Lymph node sensitivities obtained using multi-detector CT with contrast enhanced multiplanar reconstruction has been more promising. Filippone et al. (2004) showed a sensitivity of detection of lymph node metastases of 90% in 41 patients and by comparison, Kanamoto (2007) 87% in 51 patients. However the use of size as the main criterion for diagnosis will remain problematic. This is emphasised by Hundt and colleagues (1999) who showed that 11 out of their 34 cases underestimated the N stage due to microscopic involvement of the lymph nodes without enlargement, giving a CT sensitivity of 68%.

CT scan was not originally utilised to provide information regarding local staging of colonic tumours. CT scan has technique-related limitations that make the distinction between T1 and T2 tumours difficult and in future studies they may be needed to be looked together as a joint T1-T2 group. Dighe and colleagues (2010) evaluated the accuracy of multidetector CT in stratifying patients with colon cancer in good and poor prognostic groups. Low risk groups included patients with T1/T2 tumours and also T3 tumours with extramural depth of less than 5 mm. High risk groups included T3 tumours with extramural depth greater than 5 mm and T4 tumours (The cut off of 5mm for extramural depth had been shown previously by Smith and colleagues (2007) to be a good distinction between good and poor prognosis according to histopathology and disease free survival). The authors reviewed CT scans of 84 patients and showed an accuracy of 74% for T staging of colon cancer with sensitivity of 78% and

specificity of 67%. Furthermore they noted worse accuracy for detection of malignant lymph node at 58%. Overall, agreement for assigning patients into either a good or poor prognosis group was moderate with kappa value of 0.54. The authors argued for a role of preoperative CT in the identification of patients suitable for recruitment for the UK national FOxTROT trial entitling patients with poor prognosis features neo-adjuvant chemotherapy. With this in mind, it is of some concern to note that in their series, 10 out of 30 tumours with favourable eventual histological features were deemed to be radiologically poor prognosis and thus would potentially over treated with neo-adjuvant chemotherapy. On the other hand, 12 out of 54 tumours with a poor prognosis on histology were judged to be of good prognosis radiologically.

Leufkens et al (2011) also conducted a systematic review of the accuracy of colon cancer staging by Computed Tomography. They excluded all studies with rectal cancer staging and those that did not have a separate analysis for colon cancer staging. Only 11 studies were included in the review with 753 patients in total. Sample-size-weighted sensitivity, specificity and accuracy for T-staging was 77%, 3% and 67%, respectively; and for N-staging 76%, 55% and 69%, respectively. The specificity for T staging was considerably low and probably related to the difficulty of CT interpreting individual layers of the colonic wall particularly in the presence of poor preparation and absence of rectal insufflation. Limitations of this review are that the number of included studies was small, reviewing radiologists were aware of the diagnosis or information on blinding was not stated in the study, and 5 of the 11 studies were retrospective in design. There is much heterogeneity in the CT protocol used for local staging of colonic cancers and in this review, only a third of the studies offered CT axial imaging at 5mm slices. Another additional technical aspect is that if multiplanar reconstruction is not used routinely to locally stage the tumour, then true axial images must be obtained which are through the tumour and perpendicular to its long axis. Anderson and colleagues (2011) assessed the effect of true axial imaging on the accuracy of colonic cancer staging. 50 consecutive datasets were consecutively assessed by 3 radiologists. The images were read as standard axial CT initially and then re-read 6 weeks later but with true axial slices through the tumour and perpendicular to the long axis. The overall accuracy for tumour (T) staging was 56% for Radiologist 1, 48% for Radiologist 2 and 64% for Radiologist 3 for standard axial CT imaging. This improved to 72% ($p=0.012$), 66% ($p=0.012$) and 80% ($p=0.021$)

when the true axial images were added. Similarly, for nodal staging, overall accuracy improved from 56% to 70% ($p=0.065$) for Radiologist 1, 58% to 76% ($p=0.012$) for Radiologist 2 and 60% to 76% ($p=0.021$) for Radiologist 3 when true axial images were used.

In our study, only one radiologist was responsible for the interpretation of CT images which limited our analysis. This was a prospective study, therefore all images were analysed pre-operatively removing biased which may have been imposed on a retrospective analysis. For subsequent analyses of future CT images, we have assigned 2 radiologists to interpret the images independently and we plan to compare the inter-observer variability of local staging.

Currently, local staging of colonic cancer does not affect the treatment outcome in patients as all patients deemed fit for surgery are offered segmental resection based on the absence of distant metastases rather than local staging. However, the possibility of neo-adjuvant chemotherapy for advanced colonic cancers may increase the importance of accurate local staging and with this in mind; we embarked on this prospective study. In the future, distinction between T3 and T4 tumours from T1 and T2 tumours may have more importance and both colonoscopic high frequency ultrasound and CT should be able to offer this. It would be interesting to apply colonoscopic high frequency ultrasound as an additional staging arm to FOxTROT as our initial results are somewhat promising and this may play a role in the future in the local staging of colon cancer.

4.5 CONCLUSIONS

Accurate pre-operative staging of colonic cancer is important for optimising treatment. Local staging of tumours has been shown to be important in rectal cancer, currently in colonic cancer the focus is on CT staging of distal metastases. There is a possibility that the role of neo-adjuvant chemotherapy might expand to include colonic cancer. Also the introduction of laparoscopic surgery for colonic resections increases the significance of local staging since T1 and T2 tumours are more suitable for laparoscopic surgery. We have shown in this small prospective comparison that high frequency mini probe endoscopic ultrasound is feasible in the local staging of colonic cancers. This study comparing conventional CT and high frequency ultrasound for local staging of colonic cancer shows that both 12 and 20 MHz ultrasound are significantly better for T staging of colonic cancer, with 12 MHz only being advocated for detection of nodal disease. These findings need to be evaluated further and confirmed in a larger scale study.

CHAPTER 5

Endoscopic ultrasound and rectal tumours

CHAPTER 5

5.1 INTRODUCTION

In the last decade, ERUS has become increasingly available and accepted as a tool for staging rectal cancers. The technique has in the past been less utilised as the modality as it requires a significant learning curve for orientation and identification of ultrasound images and planes. Intraluminal examination of the rectum by ultrasound can be done using a rigid probe or a flexible echoendoscope. High frequency mini probes are also now available which can advanced through the working channel of standard colonoscopes and image tumours under direct endoscopic vision.

The accuracy of ERUS for assessing depth of invasion of rectal cancer (T stage) ranges from 80-85%, compared to 65-75% for CT and 75-85% for MRI (Gleeson 2009). A recent meta-analysis pooling studies from 1980 to 2008 (Puli et al 2010) showed that sensitivity and specificity of ERUS to diagnose T1 cancers were 87.8% and 98.3% respectively. Results for the other stages for sensitivity and specificity were 80.5% and 95.6% for T2 tumours; 96.4% and 90.6% for T3; and 95.4% and 98.3% for T4 tumours. ERUS has been shown to be particularly accurate for staging superficial tumours. Zorcolo and colleagues (2009) found that ERUS differentiated early and advanced rectal cancers with 96% sensitivity, 85% specificity and 94% accuracy.

Local excision of rectal tubulovillous adenomas at colonoscopy is often difficult as these tumours are broad based and the completeness of resection is problematic. Additionally there has been some concern regarding local recurrence after piecemeal endoscopic resection. However these issues have been minimised with the introduction of Transanal Endoscopic Microsurgery (TEMS) (Buess et al. 1988). The advantage of local as opposed to radical surgery is that it reduces patient morbidity and improves functional outcome. TEMS may be a suitable alternative operation for patients with comorbidities and high peri-operative risk. Local excision using TEMS may also be used with curative intent in patients with early rectal cancers. However, risk of local

recurrence and lymph node metastases increases with increasing depth of invasion varying from 0-18% in T1 tumours and 17-47% for T2 tumours (Kim 2000). Kikuchi et al (1995) elaborated on this and demonstrated that local lymph node involvement rates varied from 0%, 5% and 25% for sm1, sm2 and sm3 lesions respectively.

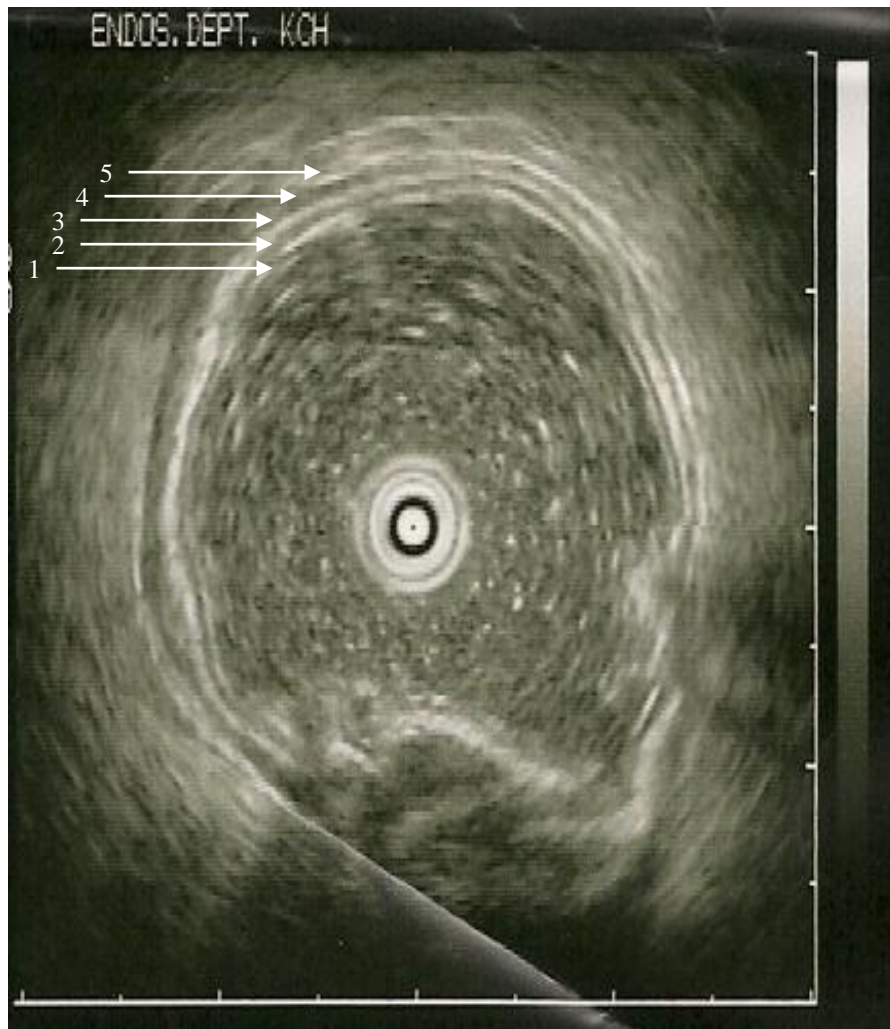
TEMS is indicated in certain patients with biopsy proven benign tubulovillous adenomas. However, surgical histopathology reveals post excision carcinoma in 21-34% of such cases (Doornebosch et al. 2008; Galandiuk 1987; Taylor 1981). EUS may raise suspicion of malignancy in the presence of benign biopsies. There is some evidence that previous TEMS procedures may increase the morbidity of subsequent radical surgery (Baron 1995; Friel 2002; Hahnloser 2005). Therefore it is vital that accurate pre-operative staging is available for all patients undergoing local excision with TEMS.

The assessment of nodal metastases is less accurate with ERUS than for tumour depth. Puli et al (2010) combined 35 studies with 2700 patients and showed that the sensitivity and specificity of ERUS for diagnosing nodal involvement was 73.2% and 75.8% respectively. There is wide variation in the literature and this is partly due to the variable criteria used for defining nodal metastases. Small nodes are not always easily observed with ultrasound and 18% of lymph nodes less than 5mm harbour metastatic disease (Skandarajah 2006). Recently, Gleeson and colleagues used ERUS with fine needle aspiration to identify suspicious nodal characteristics. They identified that nodal hypoechogenicity and short axis greater than 5mm were independent factors for malignancy. In addition, a long axis greater than 9mm was 95% specific for the presence of malignancy.

Traditional endorectal ultrasound offers accurate assessment of the depth of invasion in early rectal tumours with an overall accuracy of 87% and a sensitivity and specificity of 93% and 78%, respectively. This compares with MRI which offers 82%, 86% and 77% corresponding values (Kwok 2000). Rigid transrectal ultrasound (7.5-12 MHz), however, is not feasible in all patients due to tumours being further proximal to the dentate line and stenosis. In addition, this involves a further procedure to the diagnostic endoscopy. The potential advantage of high frequency miniprobe ultrasound is that this can be performed at the index endoscopy (by inserting the probe through

the working channel of colonoscope) and avoids the need to arrange an additional procedure. The higher frequency (20MHz) may provide superior imaging offering differentiation between mucosal and submucosal lesions (Figure 5.1).

Figure 5.1: Layers of the rectal wall with 20 MHz mini probe ultrasound



1-mucosa; 2- muscularis mucosae; 3- submucosa; 4- muscularis propria; 5-serosa

The purpose of this study was to determine the feasibility and accuracy of 20MHz mini probe ultrasound in the assessment of rectal wall penetration of tumours deemed suitable for TEMS and compare these findings to MRI and histopathology.

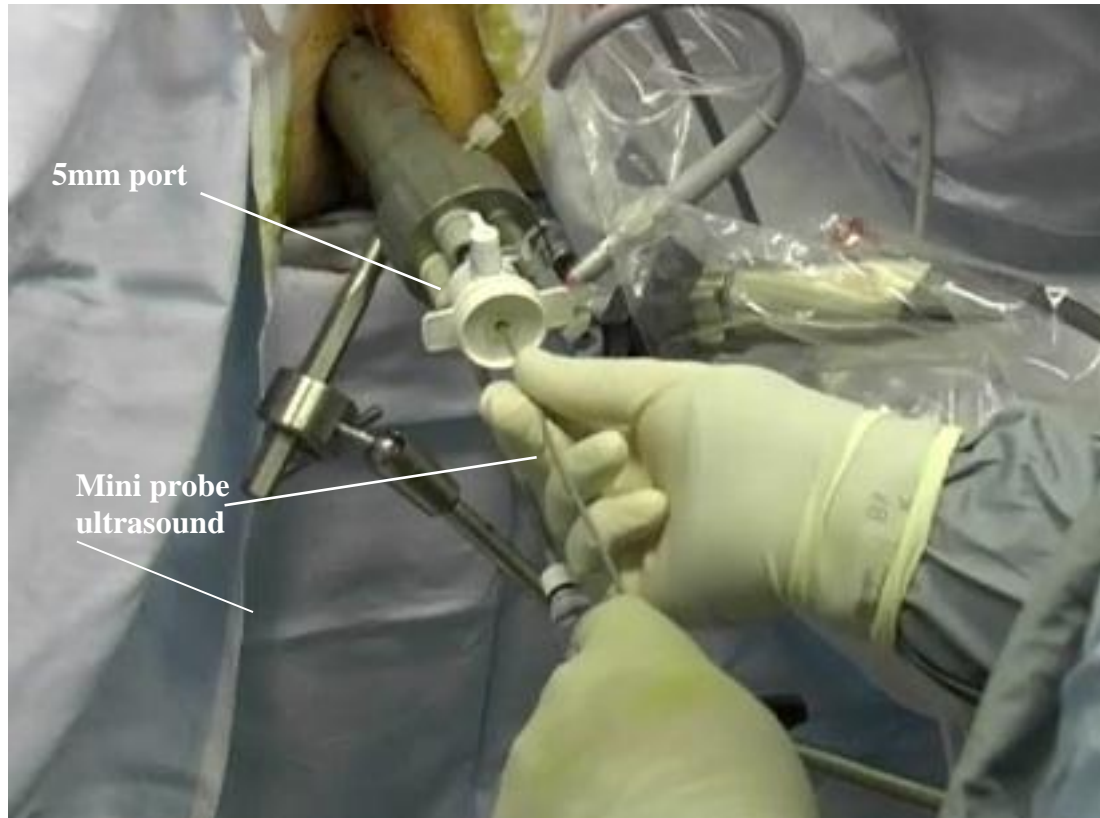
5.2 METHODS

Consecutive patients with rectal tumours deemed suitable for TEMS were included in the study from Feb 2008 to Nov 2009 after informed written consent. Pre-operative investigations in all patients included colonoscopy and biopsy, MRI of the anorectum and pelvis and 20 MHz mini probe ultrasound.

MRI was performed using 1.5T full body scanner with the patient in the supine position using a phased array surface coil centred on the pelvis. Bowel preparation and air insufflation were not used. Axial T1 weighted conventional spin echo images of the pelvis were first obtained with 4mm section thickness using a 24cm field of view. Both axial and sagittal T2 weighted fast spin echo images were then obtained in the same region using 5mm section thickness. These T1 and T2 images were then utilised to plan T2 weighted 3mm section thickness transverse oblique true axial imaging through the rectal tumour and mesorectum. The images were interpreted by an experienced colorectal radiologist pre-operatively, blind to both the ultrasound and histopathological staging.

20 MHz mini probe ultrasound examinations were performed at the index colonoscopy and during the TEMS resection by inserting the probe through the working channel of the operating scope (Figure 5.2). A 5mm laparoscopic port was used for insertion of the miniprobe to provide an air tight seal. Acoustic coupling was achieved by suctioning of excess air in the rectum and instillation of water to submerge the tumour. The main author was responsible for performing and interpreting the ultrasound images and was unaware of the results of the MRI. Images were captured on photographic paper and SVHS for further review if necessary. Another surgeon carried out all of the TEMS procedures and the specimen was resected en bloc and sent for histological analysis in formalin.

Figure 5.2: Mini probe ultrasound inserted through working channel of operating rectoscope during TEMS



Staging by ultrasound and MRI were compared to the postoperative histological resection specimen. Graph Pad Prism (Version 5) and SPSS (Version 16.0) were used to calculate the sensitivity, specificity, positive predictive value, negative predictive value, accuracy and kappa coefficients of each imaging modality against the histopathological gold standard.

Weighted kappa coefficient were used to quantify the level of agreement between the different methods with the gold standard (histopathology) in order to penalise for the amount of the disagreement observed and to allow for particular combinations of ratings not being observed. The kappa coefficient was used to quantify the level of agreement between the different methods with the gold standard (histopathology). The kappa coefficient used weights of 1, 0.5 and 0 to penalise for the amount of the disagreement observed and it also allowed for particular combinations of ratings not being observed.

5.3 RESULTS

Thirty four patients were recruited for the study, with higher proportion of males to females (20M: 14F) and mean age of 69 years (SD 14, 27-89 years). Mean Body Mass Index of the group was 26.4 (SD 5.2, range 17.6-41.6). The size of the rectal lesions ranged from 10-60 mm with a mean of 30 mm and occupied 5-55% of the rectal circumference. All lesions were below the peritoneal reflection, 5-15 cm (mean 10 cm, SD 2.6) from the anal verge.

Post-operative histology identified 21 benign tubulovillous adenomas (9 high grade dysplasia, 12 low grade dysplasia) and 13 lesions with a focus of adenocarcinoma (38%). The latter group included 3 mucosal, 7 submucosal, 2 T2 and 1 T3 tumour. In terms of T stage, there were 21 T0, 3 T1m, 7 T1sm, 2 T2 and 1T3 tumour. Therefore, 24 lesions in total were confined to the mucosa.

MRI was completed in 30/34 patients (88%) as 4 patients were unable to tolerate the investigation. MRI only identified one of the mucosal lesions, therefore these were grouped together with T1 tumours for further analysis (Tables 1-3) (Figure 5.2). There were 27 T0/T1 tumours, of which MRI correctly staged 10 (37%), over-staging 10 as T2 and 7 as T3. In addition, 4 out 10 (40%) T1 tumours were correctly staged, over-staging 5 as T2 and 1 as T3. Only two T2 tumours were present, one of which was correctly staged by MRI. In the comparison of MRI with the gold standard (histopathology) the observed agreement was 86.3%, only slightly above 84.9%, the expected chance agreement. The weighted kappa coefficient was 9% (SE=5%). No significant difference from zero was detected ($P=0.23$). Following Landis and Koch's benchmark values for the kappa coefficient this represents a very poor agreement.

Table 5.1: Agreement between MRI and histopathology for T staging of rectal tumours deemed suitable for TEMS

	mT0	mT1	mT2	mT3	Total
pT0	1	5	5	6	17
pT1	0	4	5	1	10
pT2	0	0	1	1	2
pT3	0	0	0	1	1
Total	1	9	11	9	30

p = pathological staging
m = MRI staging

Table 5.2: Agreement between MRI and histopathology for T staging of rectal tumours deemed suitable for TEMS. (T0/T1 tumours have been grouped together)

	mT0/T1	mT2	mT3	Total
pT0/T1	10	10	7	27
pT2	0	1	1	2
pT3	0	0	1	1
Total	10	11	9	30

p = pathological staging
m = MRI staging

Table 5.3: Overall accuracy of MRI in T staging of rectal tumours deemed suitable for TEMS

	Sensitivity	Specificity	PPV	NPV	Kappa
T0/T1	0.37 (0.19-0.58)	1.0 (0.29-1)	1.0 (0.69-1.0)	0.15 (0.03-0.38)	0.09 (0-0.12)

95% confidence intervals in (parentheses)
PPV=positive predictive value
NPV=negative predictive value

Acoustic coupling was achieved in all 34 patients (100%) during 20 MHz ultrasound. All 31 T0/T1 patients were correctly identified by ultrasound (100%). Within this

group, there were 24 mucosal lesions, 23 (96%) of which were correctly determined, over-staging 1 as a submucosal lesion. Additionally, 6 out of the 7 (86%) submucosal lesions were correctly identified, under-staging 1 as a mucosal lesion. 20 MHz ultrasound offered 96% sensitivity, 80% specificity and a likelihood ratio of 4.8 in differentiating between mucosal and submucosal rectal tumours. Only 2 T2 and 1 T3 tumour were present in this cohort, 2 of which were under-staged by ultrasound (Tables 4-6). In the comparison of 20MHz with the gold standard (histopathology) the observed agreement was 91.2%, well above 56.7% the expected chance agreement. The weighted kappa coefficient was 79.6% (SE=14%). This kappa coefficient was significant different from zero (95% c.i. 34% to 62%; P=0.0004). Following Landis and Koch's benchmark values for the kappa coefficient this represents moderate to substantial agreement.

Table 5.4: Agreement between 20 MHz ultrasound and histopathology for determining depth of rectal wall penetration in tumours deemed suitable for TEMS

	uMucosal	uSubmucosal	uT2	uT3	Total
pMucosal	23	1	0	0	24
pSubmucosal	1	6	0	0	7
pT2	1	0	1	0	2
pT3	0	0	1	0	1
Total	24	7	2	0	34

p = pathological staging

u = ultrasound staging

Table 5.5: Agreement between 20 MHz ultrasound and histopathology for T staging of rectal tumours deemed suitable for TEMS.

	uT0/T1	uT2	uT3	Total
pT0/T1	31	0	0	31
pT2	1	1	0	2
pT3	0	1	0	1
Total	32	2	0	34

p = pathological staging
u = ultrasound staging

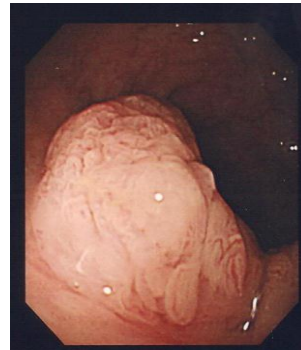
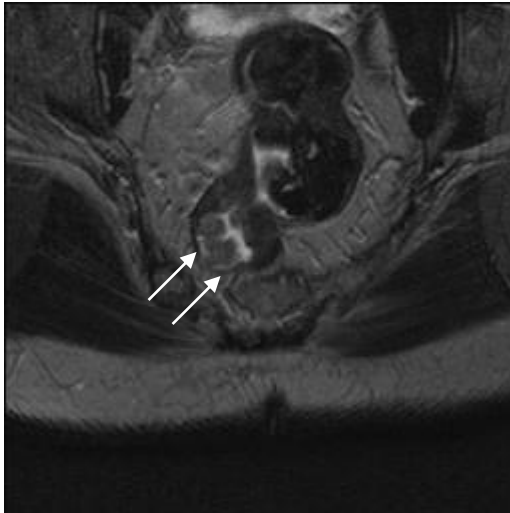
Table 5.6: Overall accuracies of 20 MHz ultrasound in T staging of rectal tumours deemed suitable for TEMS

	Sensitivity	Specificity	PPV	NPV	Kappa
T0/T1	1.0 (0.89-1)	0.67 (0.09-0.99)	0.97 (0.83-0.99)	1.0 (0.16-1)	0.79 (0.33-0.87)

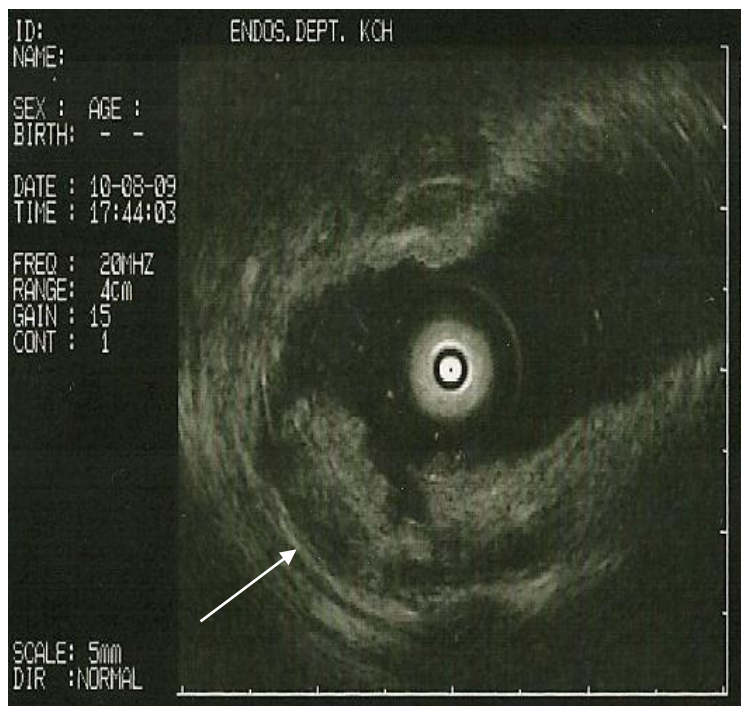
95% confidence intervals in (parentheses)
PPV=positive predictive value
NPV=negative predictive value

Overall, 20 MHz ultrasound was significantly more accurate (32/34, 94%) than MRI (12/30, 40%) in determining the rectal wall penetration for rectal tumours deemed suitable for TEMS ($p<0.0001$).

Figure 5.3: Histological stage T1 rectal tumour – comparison of MRI and 20 MHz ultrasound



MRI staged as T2 as muscularis propria not clearly separate from rectal tumour (arrow)



20 MHz US correctly staged as T1 mucosal lesion not invading the first hyperechoic submucosal layer (arrow)

5.4 DISCUSSION

Surgical excision of rectal cancers consists of either transanal excision, transanal endoscopic microsurgery (TEMs) or total mesorectal excision (TME). The choice of procedure depends on the stage of rectal cancer on pre-operative imaging which is of paramount importance as generally cancers staged as T1 or lower are treated by local excision whereas TME is reserved for more advanced stages. The usual scenario for referral for TEMs is such that a patient is discovered to have a rectal tumour with biopsies suggestive of tubulovillous adenoma with high grade dysplasia without confirmation of underlying malignancy. In our institution, we assessed these patients with both MRI and high frequency 20 MHz mini probe ultrasound to assess depth of invasion of these polyps prior to TEMs procedure. Assessment of nodal status was not assessed as the primary end point as we have previously shown that 20 MHz ultrasound is poor at assessing lymph node status and would as such made a poor comparison to MRI. Furthermore, all patients included in this study were those referred for TEMs procedure and therefore depth of infiltration of the polyp was important to ascertain as this would guide management.

MRI was utilised as a comparison to high frequency mini probe ultrasound because in our tertiary referral practice for TEMs, MRI has been used as the imaging modality of choice for the assessment of rectal tumours referred for potential TEMs. This may be an unfair comparison as the patients in this cohort were more likely to have an earlier stage of rectal tumour and MRI fails poorly in this aspect of staging. Nonetheless as this is the current practice offered in the region, we felt that any new imaging modality should be compared against the best current practice. However, it may have been more interesting to also compare the staging of these rectal tumours with traditional rigid endorectal ultrasound.

Although MRI is widely used to stage rectal tumours we show that its overall accuracy (40%) at assessing early T0 and T1 tumours compares unfavourably with that of miniprobe ultrasound which was 100% sensitive. As this cohort of patients had presumed benign tubulovillous tumours destined for TEMs procedure there is a lack of

patients with the more advanced T stages. Patients destined for TEMS were deliberately selected for this study as all of these patients would have imaging for local staging of tumour and also all patients would undergo en-bloc full excision of the tumour. Therefore, we were able to evaluate the accuracy of high frequency mini probe ultrasound in assessing depth of invasion, and compare this to MRI.

Traditionally, the ultrasonographic assessment of rectal tumours is usually undertaken by a rigid probe using frequencies between 7.5 and 12 MHz. There have been many studies that have compared the accuracy of diagnostic imaging modalities for the staging of rectal cancer but it is difficult to draw conclusions from the literature with studies varying in sample size, patient population, study design, imaging technique and results. Nonetheless, there have been two well conducted meta-analyses and a systematic review of the literature (Bipat 2004; Lahaye 2005; Skandarajah 2006) all of which point to EUS being more accurate at characterising early rectal tumours and perirectal tissue invasion, and MRI more useful in advanced disease as it was clearer in determining the anatomical planes corresponding to the mesorectal fascia (Skandarajah 2006). However, it must be emphasised that the advantages of EUS depend heavily on operator experience and transrectal EUS may be less accurate than MRI in stenotic and proximal tumours (Kulinna 2004). There is also a learning curve with operator variability. Orrom and colleagues (1990) reported an increase in diagnostic accuracy from 59.3% to 95% over a 3 year period. Some studies suggest a learning curve of 50 cases for T staging and more than 75 cases for nodal assessments (Marusch et al 2002). In our study, the author was above his learning curve for transrectal ultrasound using a rigid probe but this is our first experience of mini probe ultrasound which suggests that the skillset is easily transferable across the different probes.

Puli and colleagues (2010) performed a systematic review and meta-analysis of the T staging of early rectal tumours using endoscopic ultrasound. Patients with early rectal cancers (T0) have a high 5 year survival of greater than 95% (US National Institute of Health data 1975-2004), whereas 5 year survival for Stage II, III and IV disease are considerably worse at 65%, 35% and 9% respectively. This variation in survival makes the local staging of rectal cancer important for prognosis and treatment. The authors showed that pooled sensitivity and specificity of EUS for T0 tumour invasion was 97%

thereby allowing physicians and surgeons to correctly identify patients suitable for endoscopic treatment.

The experience of mini probes in assessing depth of invasion is limited in the literature. We determined the depth of mural invasion using 20 MHz mini probe through the working channel of the colonoscope and differentiation between mucosal from submucosal lesions was possible with an accuracy of 96%, something which is highly problematic using 12 MHz (Glancy et al. 2005). Hurlstone and colleagues (Atkinson 2007; Hurlstone 2005; Hurlstone 2005) have consistently shown high accuracy in assessing depth of invasion of colorectal polyps prior to endoscopic resection using 12.5 and 20 MHz miniprobe ultrasound. They subjected 82 lateral spreading tumours to high frequency miniprobe ultrasound and magnification chromoscopic colonoscopy. All 15 of the tumours invading the muscularis propria (T2 tumour) were accurately identified with 20MHz ultrasound and therefore not subjected to endoscopic mucosal resection. The same Sheffield group showed 93% overall accuracy in determining depth of invasion in 62 patients with flat colorectal cancerous polyps using 20 MHz ultrasound. Furthermore, the accuracy for sm1, sm2 and sm3 lesions were 100%, 92% and 93%, respectively and this group is the only group that have been able to differentiate sm1-3 lesions in the literature. Overall, their data are similar to our results of 96% sensitivity in differentiating between mucosal and submucosal lesions. We did not sub classify the tumours with submucosal invasion into ultrasonographic sm1, sm2 and sm3 but only utilized the mini probe to differentiate between mucosal and submucosal lesions. My personal experience regarding submucosal invasion is that it is extremely difficult to obtain reproducible images of the submucosal layer in order to be confident in diagnosing sm1, sm3 and sm3 lesions with 20 MHz probes. My personal opinion is that you are able to identify lesions into the upper half of the submucosal layer and those in the lower half of the layer which could potentially guide you to make decisions regarding endoscopic treatment or colorectal resection.

The new generation MRI of external high resolution phased array surface coil systems has improved the local staging of rectal cancer. The combination of high resolution, improved signal to noise ratio and a large field of view allows detailed anatomical evaluation of the rectal wall and mesorectal fascia. Despite these advantages, overall T

staging accuracies are only 67-86% (Beets-Tan 2001; Blomqvist 1997; Gagliardi 2002; Poon 2005). These results can be attributed to the fact that MRI fares worse at staging T1 and T2 tumours than more advanced cancers. Mathur et al (2003) showed that T1 and T2 tumours were staged to an accuracy of 46% whereas T3 tumours were at 76%, which was also confirmed by others (Drew 1999, Hadfield 1997). These results are similar to ours with poor agreement of MRI with histology for T0/T1 lesions, leading to overstaging of these tumours.

The decision for undertaking TEMS is relatively straightforward in the case of an endoscopically diagnosed tubulo-villous adenoma with benign histology. However, if the biopsy reveals a focus of malignancy, over-staging to T3 by MRI of early T1 lesions confined to the mucosa or just invading sm1 level may subject these patients to potentially unnecessary neo-adjuvant treatment rather than primary local surgery. The addition of endoscopic ultrasound to evaluate these lesions has great potential as part of the accurate and routine pre-operative assessment. Rigid endorectal ultrasound has been shown to be very effective in staging early rectal tumours prior to endoscopic surgery. Puli and colleagues (2009) reviewed the literature for all studies utilizing TRUS to stage lesions confined to the mucosa (T0) all of whom had endoscopic surgery. They identified 11 relevant studies with 1791 patients. The pooled sensitivity and specificity of TRUS in diagnosing T0 involvement was 97.3% and 96.3% respectively. Furthermore, TRUS had a high positive likelihood ratio and a low negative likelihood ratio which indicates that TRUS was superior in excluding as well as diagnosing the correct histological stage. Despite these impressive results, many authors have stated that it is challenging to distinguish between T0 and T1 lesions using the rigid probe. Zorcolo and colleagues (2009) reported on 81 patients whom had undergone TRUS and subsequent TEMS. They grouped the T0 and T1 lesions together for their analysis and showed that TRUS had an overall accuracy of 94%. However, differentiation between T0 and T1 lesions was challenging with 57.6% of adenomas and 30.7% of carcinoma in situ being staged as uT1. Furthermore, almost half of the pT1 tumours were staged as uT0. The authors felt that this was not clinically relevant as in their practice all patients with T0 and T1 tumours were offered local excision by TEMS and making this differentiation was not clinically relevant.

The advantage of high frequency mini probes is that the entire lesion can be sequentially scanned under endoscopic vision of the probe ensuring that no part of the tumour is left un-staged and that it does offer the differentiation between mucosal and submucosal lesions. We cannot conclude that high frequency ultrasound should be a replacement to MRI but simply that this is feasible in the rectum with promising initial results. Therefore, it may be a useful adjunct to the assessment of rectal polyps referred for TEMS excision. Furthermore, the high accuracy in differentiating mucosal from submucosal lesions may prove useful in assessing polyps throughout the colon and rectum prior to embarking on endoscopic resection.

For future studies, it would be useful to compare colonoscopic mini probe ultrasound with traditional endorectal ultrasound using a rigid probe to determine whether mini probes could be used as an alternative staging tool, thereby providing this imaging during the initial colonoscopy rather than awaiting a second procedure.

5.5 CONCLUSION

Our results indicate that high frequency mini probe ultrasound is feasible in the rectum to evaluate tumours referred for TEMS. The accuracy of 20 MHz ultrasound is clearly superior to that of MRI in assessing depth of rectal wall penetration for T0 and T1 tumours. Ultrasound can raise suspicion of malignancy in the case of pre-operative benign biopsies. If the high diagnostic accuracy of this method is confirmed for T3 tumours then there may be a role for more accurate selection of patients with rectal cancer for pre-operative radiotherapy. Further studies are indicated especially in patients with more penetrative tumours.

CHAPTER 6

Endoscopic ultrasound and malignant colorectal polyps

CHAPTER 6

6.1 INTRODUCTION

Patients who have undergone snare polypectomy for malignant polyps are a management challenge. The decisions regarding further surgery or endoscopic surveillance are a balance between the assessments of risk of residual disease or involved local lymph nodes against the morbidity and mortality of surgical resection. Malignant polyps confined to the mucosa are not thought to pose a risk of lymphatic or haematogenous spread due to the absence of lymphatics within the mucosal layer (Fenoglio 1973)¹. However, increased risk of lymph node metastasis is proportional to the depth of invasion into the submucosa (Kikuchi 1995)². Hassan and colleagues (Hassan 2005)³ pooled data from 31 studies in the literature with 1900 patients and showed that different histological factors were linked to distinct clinical outcomes. The presence of a positive resection margin post polypectomy is predictive of local disease; poorly differentiated carcinomas are associated with higher mortality, and vascular invasion with a higher risk of lymph node disease.

Endorectal ultrasound has been utilised for risk assessment post polypectomy of malignant rectal polyps in relation to residual disease and local lymphadenopathy (Garcia-Aguilar 2005)⁴. The assessment of malignant polyps in the proximal colon using high frequency mini probes inserted through the working channel of the standard colonoscope is now possible (Maruta 1994)⁵. The colonic wall is seen as a five layered structure alternating between hyperechoic and hypoechoic signals with 12 MHz

ultrasound (Figure 1.7). The first hyperechoic layer is the interface between the water and mucosa. The second hypoechoic layer corresponds to the mucosa. The third hyperechoic is the submucosa, followed by a fourth hypoechoic muscularis propria and the outer hyperechoic serosa. Increasing the frequency to 20MHz scanning offers greater resolution of the colonic wall depicting the muscularis mucosae between the mucosa and the submucosa, and at the same time offering detailed views of the submucosa.

We offered colonoscopic high frequency mini probe ultrasound post polypectomy for malignant polyps in the colon and rectum. Here we report our initial results using such an approach as an adjunct in the management of malignant colorectal polyps.

6.2 METHODS

Consecutive patients identified as having a focus of malignancy post endoscopic snare polypectomy from March 2008 and November 2009 were entered into the study after informed written consent. The endoscopy department in our institution has a protocol to state that all polyps greater than 1 cm that have undergone endoscopic treatment should be tattooed with ink in the vicinity so that future treatment may be undertaken if deemed necessary. All patients underwent repeat diagnostic colonoscopy within 3 months of the index colonoscopy for endoscopic ultrasound assessment. Both 12 and 20 MHz (Olympus Keymed UM-3R, Japan) mini probe high frequency ultrasound was performed in a back to back design to check for local recurrence and local lymphadenopathy. Acoustic coupling was achieved during colonoscopic ultrasonography by suctioning of excess air, and water instillation in the colon to submerge the area of interest completely. Images were captured and real time ultrasound recorded onto SVHS to enable further review if necessary. During colonoscopic examination, the presence of residual abnormality was noted and biopsies were taken from any macroscopically abnormal area. Ultrasound examinations were undertaken in all patients in the vicinity of the previously tattooed area, and residual abnormalities were defined as mucosal, submucosal or invading into muscularis propria. In addition, the colonic wall layers were noted either to be intact or disrupted.

All patients underwent 64 slice CT of the chest/abdomen and pelvis using intravenous and oral contrast with multiplanar reconstruction conducted by an experienced Colorectal Radiologist. The purpose of the examination was to detect the presence of

local mesenteric lymphadenopathy and distant metastases. Nodal metastases or positivity on CT was defined as either a single node greater than 1 cm or a cluster of 3 nodes each greater than 3 mm. With respect to high frequency ultrasound, size was not a criterion and well defined hypoechoic nodes were taken as positive. The colorectum was scanned sequentially in the vicinity of the previously tattooed area and 10 cm above and below this region to evaluate for local lymphadenopathy.

The follow up protocol for all patients consisted of clinical assessment in the colorectal cancer follow up clinic at 3, 6 and 12 months. History, clinical examination, serum carcinoembryonic antigen levels were performed at each visit. Repeat colonoscopy was performed at 6 and 12 months. Further 64 slice CT of the abdomen/pelvis and chest was performed at 12 months. Thereafter, patients were followed up in the colorectal cancer follow up clinic with 6 monthly clinical visits, a further CT scan at 24 months and a colonoscopy at 3 years.

6.3 RESULTS

Twenty one patients were recruited into the study with a mean age of 67 (SD 13.7, range 27-86). The male to female ratio was 15M: 6F. The location of polyps in the colorectum included rectum (n=8), sigmoid (n=10), transverse colon (n=1), ascending colon (n=1), and caecum (n=1). There were 6 pedunculated and 15 sessile polyps. The mean size of the polyps was 26mm (SD 12, range 12-50 mm). (Table 6.1)

All patients had a focus of adenocarcinoma within the polyp: 12 of these were well differentiated adenocarcinomas confined to the mucosa; and 9 infiltrated into the submucosa (7 within the sm1 layer and 2 into sm2). All patients had successful endoscopic polypectomy without complications with complete histological margins in 12 cases, incomplete in a further 4 and uncertain margins in the remaining 5 cases due to diathermy artifact.

12 and 20 MHz colonoscopic high frequency ultrasound was undertaken in all twenty one patients with successful acoustic coupling. Macroscopic endoscopic residual abnormality at the previous polypectomy site was seen in 8 patients. 20 MHz ultrasound revealed all 8 of these abnormalities to be contained within the mucosa as mucosal irregularity with intact normal colonic wall layers (Figure 6.1 and 6.2). The remaining 13 patients had normal 20 MHz ultrasound. None of the patients were observed to have local lymphadenopathy using 12 MHz ultrasound scanning.

Figure 6.1a-c: Endoscopic and ultrasonographic images of a post polypectomy site showing scar tissue endoscopically and intact normal colonic wall layers on 12 MHz and 20 MHz ultrasound



Fig 6.2a: Endoscopic view

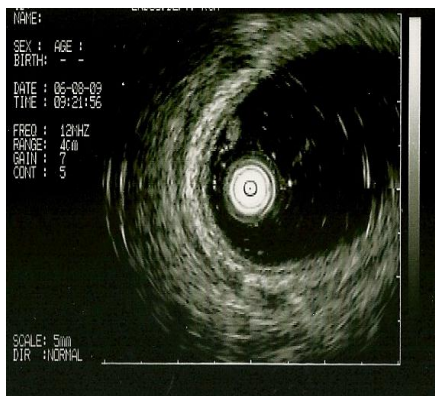


Fig 6.2b: 12 MHz ultrasound

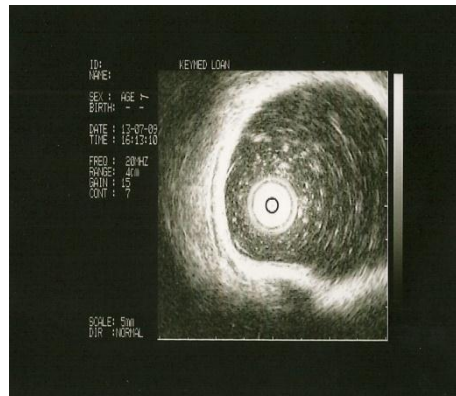
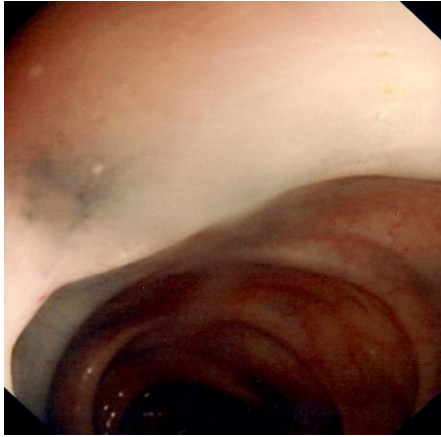
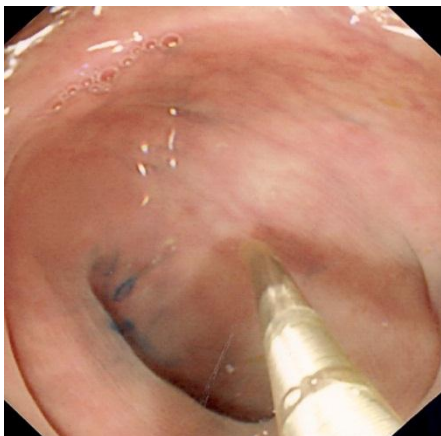


Fig 6.2c: 20 MHz ultrasound

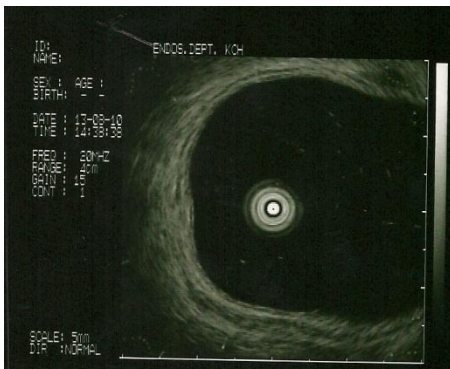
Figure 6.2a-c: Endoscopic and ultrasonographic images of a post polypectomy site showing scar tissue endoscopically and intact normal colonic wall layers on 20 MHz ultrasound



a. Endoscopic view showing polypectomy scar



b. High frequency ultrasound probe through working channel of colonoscope



c. 20 MHz ultrasound image showing intact colonic wall layers with no suggestion of recurrence

Table 6.1: Tumour characteristics of the 21 endoscopically treated polyps

Patient No.	Age	Location of polyp	Size of polyp/mm	Type of polyp	Depth of malignancy	Differentiation	Resection margin	Further surgery
1	76	RECTUM	20	TV	intramucosal	Well	INCOMPLETE	No
2	59	SIGMOID	17	TV	intramucosal	Well	COMPLETE	No
3	67	TRANSVERSE	15	TV	sm1	Well	COMPLETE	No
4	79	SIGMOID	40	T	intramucosal	Well	INCOMPLETE	No
5	77	RECTUM	14	TV	sm1	Well	UNCERTAIN	Yes
6	58	RECTUM	30	TV	intramucosal	Well	INCOMPLETE	Yes
7	79	SIGMOID	25	T	intramucosal	Well	UNCERTAIN	No
8	52	SIGMOID	15	T	intramucosal	Well	COMPLETE	No
9	78	CAECUM	20	TV	sm1	Well	INCOMPLETE	Yes
10	70	SIGMOID	25	T	intramucosal	Well	COMPLETE	No
11	51	SIGMOID	35	T	intramucosal	Well	COMPLETE	No
12	67	SIGMOID	40	TV	intramucosal	Well	COMPLETE	No
13	27	RECTUM	50	T	sm1	Well	UNCERTAIN	Yes
14	79	RECTUM	50	TV	intramucosal	Well	COMPLETE	No
15	72	RECTUM	15	TV	sm2	Well	UNCERTAIN	No
16	76	ASCENDING	30	TV	intramucosal	Well	COMPLETE	No
17	69	RECTUM	24	TV	intramucosal	Moderate	UNCERTAIN	Yes
18	68	SIGMOID	12	TV	sm2	Well	COMPLETE	Yes
19	50	SIGMOID	20	TV	sm1	Well	COMPLETE	No
20	61	RECTUM	40	TV	sm1	Well	COMPLETE	No
21	86	SIGMOID	15	TV	sm1	Well	COMPLETE	No

Tv=tubulovillous; T=tubular; sm1/2 = Kikuchi level for depth of submucosa invasion to upper 1/3 and middle 1/3 respectively

Incomplete resection margin defined as within 1mm of the edge of the tumour; Uncertain margin related to diathermy artifact

The eight patients with a macroscopic abnormality endoscopically had biopsies taken from this site, all of which were deemed to be hypertrophic scar tissue on histological analysis.

Mean follow up for patients in this cohort was 44 months (1-59 months). All patients had normal CT imaging of their abdomen/pelvis and chest. 15 out of 21 (72%) patients were managed conservatively and did not undergo surgery after an informed discussion with the patients. All of these patients have remained disease free with normal subsequent colonoscopy and CT. 6 out of 21 (28%) patients underwent further colorectal resection (Table 6.2). All 6 of these patients had normal follow up endoscopy, 12 and 20 MHz ultrasound and normal CT imaging. Examination of the resected surgical specimen histologically revealed absence of cancer. Two of these patients had protracted length of stay due to post-operative complications, the first developing multi-organ failure secondary to sepsis and the second developed acute respiratory distress syndrome secondary to lower lobe pneumonia.

Table 6.2: Outcome of patients with malignant polyps scheduled for surgery

Patient	Age	Polyp location	Polyp size /mm	Cancer invasion	Resection margin	Surgery	LOS / days
1	77	Rectum	14	Sm1	Uncertain	TEMS	1
2	78	Caecum	20	Sm1	Incomplete	RH	9
3	28	Rectum	50	Sm1	Uncertain	AR	37
4	58	Rectum	30	Mucosal	Incomplete	TEMS	1
5	69	Rectum	24	Mucosal	Uncertain	TEMS	1
6	68	Sigmoid	12	Sm2	Complete	SC	97

Sm1/2=submucosal invasion, Kikuchi level1/2

TEMS= Transanal endoscopic microsurgery

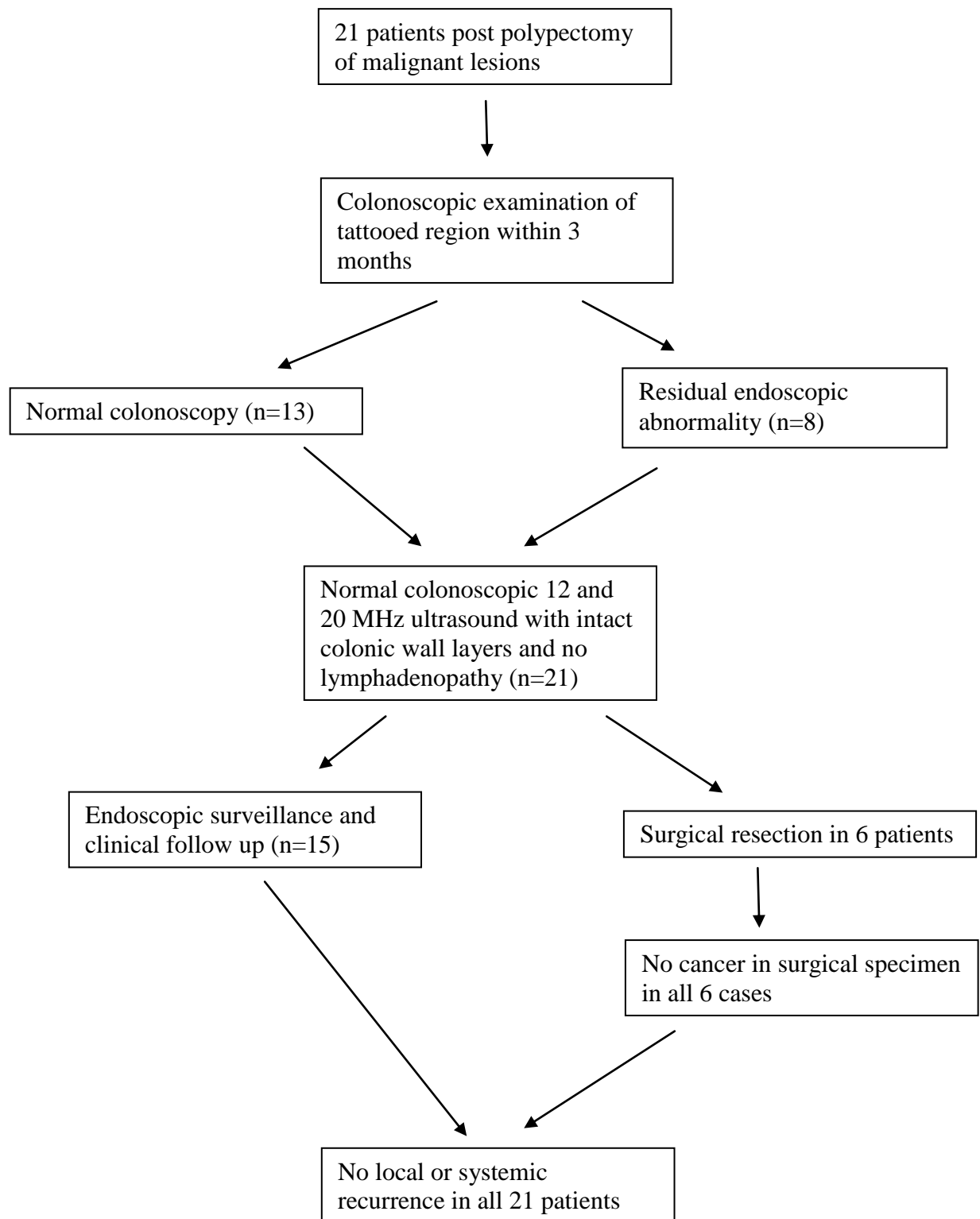
RH= Right hemicolectomy

AR= Anterior Resection

SC= Sigmoid colectomy

LOS= length of stay

Figure 6.3: Flow chart to demonstrate outcome of patients with malignant polyps



6.4 DISCUSSION

Our initial experience indicates that most patients with apparent local malignant colorectal polyps can be managed after endoscopic polypectomy without the need for major surgery. This is suggested by the observation that all patients within this cohort did not show evidence of local or systemic recurrence. The 6 patients who underwent radical surgery after an informed consent process did not have any evidence of residual disease in the resected surgical specimen. Radical surgery is not without complications, especially that for rectal resection (Grumann 2001; Karanjia 1992; Lewis 1992) and autonomic nerve injury and sexual and urinary dysfunction is common (Havenga 1996). Therefore, the decision for radical surgery after endoscopic treatment of malignant polyps should be with caution.

Traditionally, assessment of malignant polyps for prediction of residual disease and local lymphadenopathy has been by histology. Histological parameters such as positive resection margin, poorly differentiated adenocarcinoma and vascular invasion are all associated with poorer outcome in terms of local recurrence and lymph node metastases (Hassan 2005). Histological margins are often difficult to assess especially after piecemeal polypectomy of sessile polyps (Colacchio 1981; Haggitt 1985; Morson 1984). The level of confidence having clear margins range from 82-100% in different series (Colacchio 1981; Morson 1984; Haggitt 1985). Endoscopic ultrasound has therefore been used as an aid to assess for the presence of residual disease and local lymphadenopathy. All previous studies have been in the rectum. Kruskal and colleagues (1999) reported a sensitivity of 100% and specificity of 44% for endorectal ultrasound in detecting residual cancer in 13 patients whom had undergone

polypectomy for rectal malignant polyps. Garcia-Aguilar et al (2005) showed an accuracy of 90% in the assessment of residual disease at the polypectomy site. However, the negative predictive value was 86% indicating that a normal ultrasound does not exclude the possibility of residual cancer in the surgical specimen. We showed normal 12 and 20 MHz ultrasound at the polypectomy site in all 21 patients. Although, none of these patients have developed local recurrence, 6 of them underwent surgery allowing direct comparison with histological assessment of the resected specimen. In our initial experience, a macroscopic abnormality on endoscopic view was frequently detected and these could be evaluated further with ultrasound. The abnormalities were limited to the mucosa with maintenance of the colonic layers suggesting that this was related to previous resection artifact rather than residual disease. The ultrasound images of surgical scar, diathermy artifact and residual disease need to be evaluated further in a series with a larger sample size in order for us to come to some definite conclusions. Nonetheless, we have shown that high frequency mini probe ultrasound is feasible in the colon and rectum and may be a promising application in the future management of malignant colorectal polyps.

6.5 CONCLUSION

High frequency mini probe ultrasound is feasible in the colon and rectum for the assessment of the polypectomy site post endoscopic resection of malignant polyps. Definitive management of these polyps cannot be exclusively based on the ultrasound findings but this may act as a useful adjunct to histology in providing a more complete prediction of poorer prognosis.

CHAPTER 7

Endoscopic ultrasound and diverticular disease

CHAPTER 7

7.1 INTRODUCTION

Diverticular disease is characterised by outpouchings of the colonic wall through areas of natural weakness affecting over half of the population of the United Kingdom, ranking it as one of the most common bowel disorders of the Western world. The majority of patients remain asymptomatic but a minority of individuals may develop associated morbidities ranging from excessive flatulence through to diverticulitis (Eggenberger 1999). Diverticulitis may lead to further complications such as abscess formation, colonic perforation and large bowel obstruction in up to 25 % of patients (Kang et al. 2004). Prevalence in Northern Europe ranges from approximately 13% in patients up to the age of 54 to 40-50% in elderly patients over 75 years (Eide 1979, Parks 1982). The age standardised mortality has not changed considerably in the United Kingdom over the last 3 decades (Kang et al 2003) but as this is an age related disease, the burden on society will increase as the life expectancy increases in our population (UK Office for Statistics 2007).

The mechanical features of the bowel are maintained via circular and longitudinal muscular layers. The circular muscle is responsible for peristalsis and the longitudinal muscles condense in thick bands which pull the colon into a relatively short length. In diverticular disease the circular muscle is thicker and the longitudinal muscle is shorter (Eggenberger 1999). This muscle thickening is not due to hypertrophy (Haber et al. 2000), but to deposition of collagen and elastin (Whiteway 1985; Golder et al 2007; Eastwood 2003). Interestingly, the pre-diverticular state is thought to consist of the muscle abnormality alone, even without the presence of diverticula and the identification of such colonic abnormalities may explain symptoms in some patients.

Assessment of diverticular disease is conventionally performed using colonoscopy with cross sectional imaging reserved for assessment of diverticular complications. Colonoscopic assessment can identify the number of diverticula in the colon and also evaluate the superficial changes in the bowel mucosa. Recent advances in

colonoscopic ultrasound have made it possible to evaluate the colorectal wall in detail. High frequency (20 MHz) mini probe ultrasound has been used to evaluate the colorectal wall in patients with Ulcerative Colitis (Tsuga et al. 1998), but this has not been evaluated in patients with diverticular disease. The aim of this study was to determine the feasibility of high frequency ultrasound in the assessment of diverticular disease, in particular to assess the colonic wall thickness in symptomatic diverticular patients and compare these to normal asymptomatic patients.

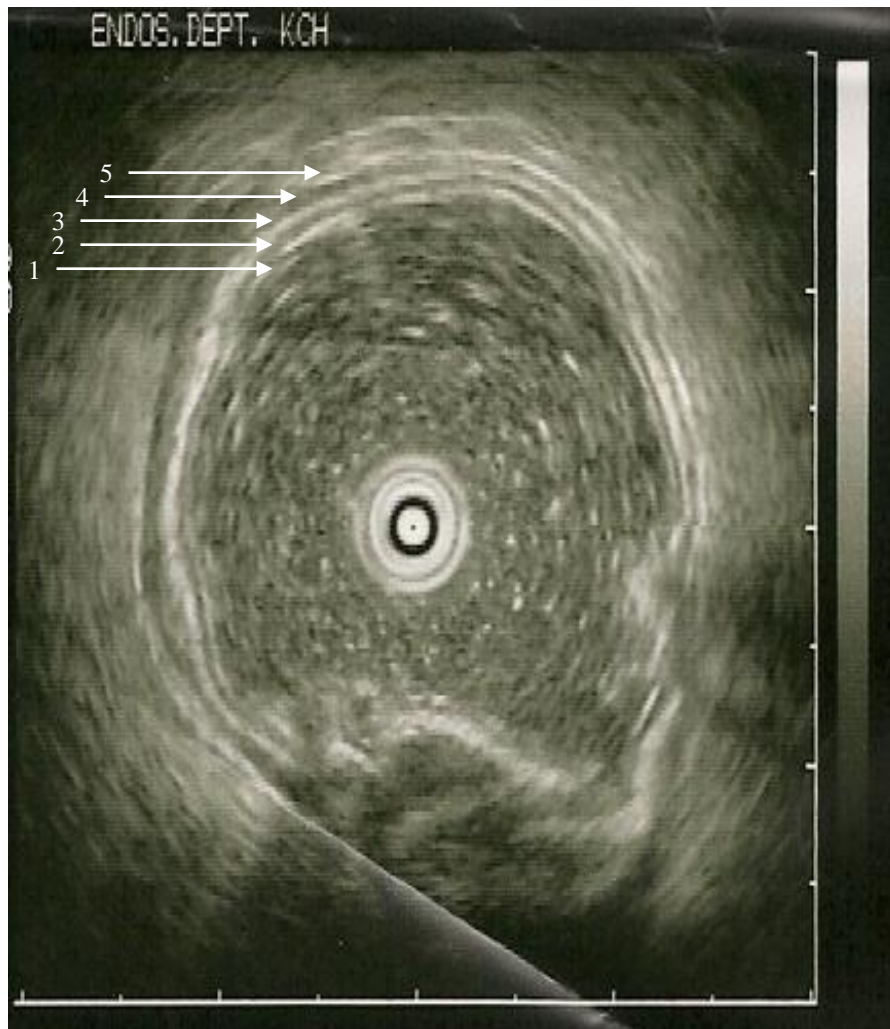
7.2 METHODS

Patients were recruited from the Colorectal Outpatient department in our institution. These were patients that were referred to a Specialist Diverticular disease clinic who were assumed to have symptomatic uncomplicated diverticular disease. Symptoms of these patients included lower abdominal pain and bloating, rectal bleeding and tendency to pass small pellet type stools per rectum. All patients with complicated diverticular disease were excluded such as those with previous confirmed localised perforation, diverticular stricture or fistula, previous pericolic or pelvic abscess or patients who had undergone previous surgery for diverticular disease. In addition, patients who simply had the presence of diverticula and whom were asymptomatic were also excluded from the study.

After initial informed consent, all patients underwent diagnostic colonoscopy and 20 MHz (Olympus Keymed UM-3R, Japan) mini probe high frequency ultrasound was performed during the same procedure if sigmoid diverticular disease was encountered.

Demographic data, severity and distribution of diverticular disease, and high frequency ultrasound findings were collected for all patients in the study. Only patients with isolated sigmoid diverticula were included in the study. The severity of diverticular disease was divided into mild, moderate and severe depending on the number of populated diverticula, less than 10, 10-25, and greater than 25 respectively. The thickness of the colonic wall was measured in the mid sigmoid colon for all patients using 20 MHz high frequency ultrasound (Figure 7.1). The mini probe was introduced through the working channel of the colonoscope to measure the thickness of the colonic wall. The mini probe was applied perpendicular to the colonic wall in order to take accurate measurements of the different layers of the colon. Acoustic coupling was achieved during colonoscopic ultrasonography by suctioning of excess air, and water instillation in the colon to submerge the area of interest completely. Images were captured and real time ultrasound recorded onto SVHS to enable further review if necessary.

Figure 7.1 20 MHz colonoscopic ultrasound showing the layers of the colonic wall in detail.



1-mucosa; 2- muscularis mucosae; 3- submucosa; 4- muscularis propria; 5-serosa

The structure of the colonic wall was evaluated with reference to the total wall thickness, mucosa, submucosa and muscularis propria. The ultrasound images were captured as still frames and measurements of the individual layers of the colonic wall were taken in millimetres (mm) using the EUM 30 processor twin point “on screen” callipers (Keymed). The 20 MHz UM-3R catheter probe (Olympus, Keymed) provides a B-mode 360 degree radial image in a perpendicular plane adjacent to the most

proximal tip axis. Similar data was sought from normal control patients who were undergoing colonoscopy either for screening or asymptomatic patients undergoing follow up colonoscopy for polyps. Only patients with normal colonoscopic findings were included in the control group (Figure 7.2)

Figure 7.2 20 MHz ultrasound image showing an example of measurement of thickness of muscularis propria in patients with diverticular disease (calipers mark MP layer)



Patients in both groups had biopsies of the colon in the region of the ultrasound measurements to exclude other diagnoses which could confound the measurements. The time taken (mins) to perform the ultrasound examination was recorded from the insertion of the probe to its withdrawal from the working channel of the colonoscope. In addition, for both groups of patients, quality of life data was measured using two different health survey instruments. An institution specific “Bowel disease questionnaire” (see Appendix 2) was utilised to assess the impact of the symptoms (if any) on the patients’ lifestyles and perceptions of their general health. There were 32 questions which evaluated four different areas: bowel symptoms, systemic symptoms, emotional and social function. Patients were asked to categorise the impact on a scale from 1 (severely affecting their life) to 7 (normal or minimal affect). The second survey was the Short Form 36 (SF-36) questionnaire (see Appendix 1) which is a self-completed questionnaire covering broad aspects of health. There questions on functional status, emotional and social well -being. The overall evaluation of health are categorised in eight groups: physical function; role-physical; body pain; general health; vitality; social functioning; role-emotional; and mental health reported health. These eight are then clustered to form two higher-order scales, the physical and mental health summary scores. In comparison with other generic health indices, the SF-36 has been shown to discriminate better between populations with varying quality of life (QOL) (Chrispin 1997, Heyland 1998).

Statistical analyses were carried out using SPSS version 15 and Graphpad Prism version 5. The thicknesses of the colonic wall were compared between the two groups of patients using two sample t test and linear regression analysis adjusted for age and sex. Similar comparisons were of QOL between the two groups. For the latter, we used linear regressions to model the effect of different factors on the response total score SF36. The multivariate linear regression model, used to assess the difference between the normal and DD groups while adjusting for the concurrent effect of potential influential variables and possible interactions. Those variables with significance below 0.20 in the univariate models were fitted in the multivariate model in a stepwise manner, with final significance assessed at the usual 5% level. Differences between the two groups in terms of symptoms are assessed by two-sample t-tests.

7.3 RESULTS

There were a total of 36 patients, 17 in the normal group and 19 in the DD group. The mean age overall was 59 (SD=13; range 32 to 82). The mean age in the normal group was 56 (32-76) whereas it was 61 (43-81) in the DD group. There was no significant difference in the two groups ($p=0.27$). Of the patients in the DD group, 6 (32%) had mild, 4(21%) moderate and 9(47%) severe diverticular disease in terms of the number of populated diverticula in the sigmoid colon.

The thickness of colonic wall at the level of the mid sigmoid colon for mucosal (M), submucosal (SM), muscularis propria (MP) and total colonic wall thickness (TCWT) are shown in Table 7.1-7.3. At all levels, the thicknesses of colonic wall was significantly greater in diverticular disease patients than in normal controls which was especially predominant in the muscularis propria and total colonic wall thickness ($p<0.0001$).

Table 7.1 Thickness of the sigmoid colon in diverticular disease patients during colonoscopic ultrasound using 20 MHz mini probe

Colonic wall layers	Mean/mm	Range	SD +/-	SE	95% CI
Mucosa	0.83	0.5-1.2	0.19	0.04	0.73-0.92
Submucosa	1.25	0.6-2.2	0.38	0.09	1.07-1.44
Muscularis Propria	2.81	0.9-4.6	1.01	0.23	2.33-3.30
Total wall	5.52	2.4-8.9	1.80	0.41	4.65-6.39

Table 7.2 Thickness of the sigmoid colon in normal patients during colonoscopic ultrasound using 20 MHz mini probe

Colonic wall layers	Mean/mm	Range	SD +/-	SE	95% CI
Mucosa	0.52	0.2-1.0	0.21	0.05	0.41-0.62
Submucosa	0.77	0.4-1.4	0.28	0.07	0.63-0.92
Muscularis Propria	0.86	0.6-1.5	0.26	0.06	0.73-0.99
Total wall	2.66	2.0-3.8	0.54	0.13	2.38-2.94

Table 7.3 Comparison of mean colonic wall thickness in normal and diverticular disease patients

Colonic wall thickness /mm	Normal patients (n=17)	DD (n=19)	P value
Mucosa	0.52 +/- 0.05	0.83 +/- 0.04	0.0002
Submucosa	0.77 +/- 0.07	1.25 +/- 0.09	0.0003
Muscularis Propria	0.86 +/- 0.06	2.81 +/- 0.23	<0.0001
Total wall	2.66 +/- 0.13	5.52 +/- 0.41	<0.0001

All patients completed both a bowel disease questionnaire which was institution specific and also the SF-36 questionnaire (Appendix 2). There was no significant difference found between the normal and DD groups in terms of symptoms (Table 7.4) using the institution specific bowel disease questionnaire. These results remained after comparisons were adjusted by age and gender; significance for multivariate is shown in the last column of Table 7.4.

Table 7.4 Results of the two-sample t-test comparing the Normal and DD groups by different symptoms using the Institution specific bowel disease questionnaire

Questionnaire section	Difference	95% C.I for difference	P value	P value (adjusted*)
Bowel	-6.5	-23.8-10.9	0.45	0.50
Systemic	-4.8	-11.0-1.5	0.13	0.18
Emotional functions	-10.5	-28.1-7.1	0.23	0.27
Social functions	-5.0	-14.6-4.5	0.29	0.29

*Adjusted for age and gender

Table 7.5 shows the univariate regressions and Table 7.6 shows the final multivariate regression model for the total SF36 scores. We observed that in the univariate model, although the DD had on average 9.2 more in the total SF36 score, this difference did not reach statistical significance (P=0.37) and only gender and the bowel, systemic and emotional symptoms showed significance.

Furthermore, only gender and the systemic symptoms score retained statistical significance in the multivariate model and after adjusting for these effects the difference between the groups was better defined (Table 7.6). Men had, on average, 17.3 more in the SF36 score (95% ci 4.7 to 29.8; P=0.01). A reduction of 2.2 was observed in the mean SF36 for each unit increase in the score for systemic symptoms (coef=2.2; 95% ci 1.2 to 3.2; P<0.0001). The significant effects observed by bowel symptoms and emotional functions in the univariate model were lost in the presence of gender and systemic symptoms. After adjusting for these effects, a significant effect of group is observed. The DD group had, on average, 13.8 more in the SF36 score in relation to the normal group (coeff=13.8; 95% ci 1.1 to 26.5; P=0.04).

Table 7.5 Univariate regression analysis for total SF-36 scores

SF-36	Coefficient	95% C.I	P value
Age	-0.05	-0.84-0.74	0.90
Gender	22.85	5.22-40.48	0.01
Severity of DD			0.22
Mild vs normal	-8.1	-35.5-19.2	0.54
Moderate vs normal	15.6	-19.8-50.9	0.37
Severe vs normal	17.3	-5.8-40.5	0.13
Group DD vs normal	9.2	-11.7-30	0.37
Bowel symptoms	0.52	-0.09-1.14	0.09
Systemic symptoms	2.35	1.10-3.59	0.001
Emotional functions	0.70	0.17-1.23	0.01
Social functions	0.47	-0.65-1.59	0.39

Table 7.6 Multivariate linear regression for SF36 total

SF-36	Coefficient	95% C.I	P value
Gender	17.3	4.7-29.8	0.01
Group DD vs Normal	13.8	1.1-26.5	0.04
Systemic	2.2	1.2-3.2	0.0000

7.4 DISCUSSION

This is a pilot study which demonstrates the feasibility of colonoscopic ultrasound to measure the colonic wall thickness in patients with diverticular disease and their normal controls. The study clearly shows that it is feasible to measure the individual colonic wall layers with high frequency 20 MHz mini probe ultrasound. The thickness of the colonic wall is thicker in patients with diverticular disease than in their normal controls with especially marked difference in the thickness of the muscularis propria layer. This is consistent with the pathological findings in diverticular disease described by Morson in 1963 with shortening and thickening of the muscularis propria causing it to behave like a myostatic contracture. Autopsy studies have also described similar increases in the thickness of colonic wall in diverticular disease (Slack 1962).

The utilisation of high frequency colonoscopic ultrasound to assess colonic wall thickness in diverticular disease is original. Traditionally, thickness of colonic wall measurements were only applied to patients with acute diverticulitis with Computed Tomography used to classify severity of diverticulitis. Ambrosetti and colleagues (1993) utilised colonic wall thickness greater than 5 mm in combination with pericolic fat stranding, abscess, extraluminal air and contrast as criteria to predict severity of disease and also to predict which patients were more likely to undergo operative intervention. Patients with severe CT findings underwent operative intervention more frequently than those patients with mild findings (33% versus 15%). In addition, patients younger than 50 years of age with severe CT findings were also more likely to have recurrences or complications (Ambrosetti 1994).

There is no current imaging modality used to assess severity of diverticular disease without diverticulitis or complications and there is no evidence which correlates anatomical findings in diverticular disease with symptoms, as patients with severely populated diverticula may have relatively few symptoms whereas those with minimal diverticula may have severe abdominal pain, bloating and change in bowel habit. Furthermore, there is no data correlating thickness of colonic wall in patients with diverticular disease with symptoms. Although, this study did show worsening quality of life SF-36 scores in patients with DD compared with controls, the number in the diverticular group were too small to draw conclusions regarding the thickness of

colonic wall and SF-36 scores within the diverticular group itself. Future studies could look at correlating the thickness of colonic wall to symptoms and one could hypothesise that symptoms of diverticular disease may be attributed in part to the colonic wall thickness especially in the muscularis propria layer. This may also be useful in the future to assess colonic wall structure in patients with symptoms suggestive of diverticular disease but with no populated diverticula. Perhaps, we may be able to assess and diagnose the pre-diverticular state which may prove useful in managing these patients and instigating medical treatment early to perhaps improve symptoms and reduce rates of complications.

There have been randomised controlled trials in the literature which have evaluated the role of medical therapy to prevent complications of diverticular disease. In 2002, Tursi and colleagues randomised 218 patients with recurrent diverticulitis to rifaximin and mesalazine versus rifaximin alone. They showed that severity of symptoms and bowel habits improved significantly in the mesalazine group with a lower recurrence of diverticulitis at 2.7% versus 18% in the non mesalazine group. There have also been studies in the literature that have used mesalazine in patients with symptomatic uncomplicated diverticular disease rather than those with previous diverticulitis. All of these studies have shown some benefit in improving symptoms and bowel habits (Tursi et al. 2006; Di Mario et al. 2005; Comparato et al 2007). The rationale for using mesalazine in the treatment of diverticular disease has taken recent research interest. Pathological evidence shows that patients with symptomatic diverticular disease often exhibit microscopic inflammation of the mucosa close to diverticula. During colonoscopy, it is sometimes noted that there is diverticular inflammation without clinical evidence of acute diverticulitis (Ghorai et al 2003). In some cases, there may even be extensive inflammation, which is defined as diverticular colitis (Makapugay et al 1996). The pathogenesis of diverticular colitis is unknown and its relation to the diverticula is unclear. However, there are several hypotheses which include mucosal prolapse, relative ischemia, bacterial overgrowth, and increased exposure to intraluminal toxins and antigens secondary to faecal stasis (Shepherd 1996; Peppercorn 2004). The rationale for the use of mesalazine in the treatment of diverticular disease involves its anti-inflammatory activity such as acting as an inhibitor of cyclooxygenase, platelet activating factor synthetase and thromboxane synthetase), which inhibit the production of interleukin (IL)-1 and free radicals (Eliakim 1992;

Grisham 1994; Wood 1996). The findings of these mesalazine studies are now the subject of international multicentre randomised blinded placebo controlled trials which may offer more insight into this aspect as medical care.

Dughera et al (2004) evaluated the role of probiotics. They randomised 83 patients, whom had had previous diverticulitis treated with rifaximin, to an oral polybacterial lysate suspension containing *Escherichia coli* and *Proteus vulgaris* or control group, and showed the recurrence rate was lower in the probiotic group at 4.6% compared to 12.5% in the control group.

There was no difference noted in diverticular and normal patients' perception of quality of life using the institution specific bowel disease questionnaire in contrast to the SF-36. This may question the validation of the institution specific questionnaire as the SF-36 is a well-established tool used in Quality of Life studies internationally. A larger sample size would be needed to validate the former questionnaire formally. The SF-36 scores in the diverticular patients were clearly worse than those in the normal group which confirms that the diverticular patients were all symptomatic and in particular clearly demonstrated anatomical differences in terms of colonic wall thickness compared to their counterparts.

This initial pilot feasibility study lends a platform to future research in this field. The two groups were chosen as such with symptomatic diverticular disease and normal subjects in order to ascertain feasibility of the technique rather than to state bold conclusions. It would be interesting to evaluate several groups of patients using the same methodology: a group with diverticulosis who are asymptomatic; symptomatic uncomplicated diverticular disease group; complicated diverticular disease group within the previous 24 months; normal patients similar to our controls and patients with a diagnosis of irritable bowel syndrome (IBS). This would then enable us to evaluate a spectrum of colonic wall thicknesses ranging from normal, through IBS, diverticulosis and complicated diverticular disease. Currently, an endoscopic diverticular score does not exist which takes into account the number of populated diverticular and colonic wall thickness and it may be interesting to propose such an entity and correlate this with patient symptoms.

In our current thinking, measurement of colonic wall thickness is not clinically useful as it does not alter management of patients with diverticular disease. However, this may offer us a better understanding of patient symptoms and might define groups of patients amenable to future treatments such as that in the prevention of complications of diverticular disease. This initial study does have several limitations which include small sample size and not including patients with a spread of severity of diverticular symptoms in order to evaluate and correlate their anatomical details and symptoms scores. Nonetheless, this has developed future research in this field which may offer us more insight into this common disease.

7.5 CONCLUSION

Colonoscopic high frequency mini probe ultrasound is feasible in the colon to measure colonic wall thickness in patients with diverticular disease. There seems to be increased colonic wall thickness across all levels especially that of the muscular propria layer. This may be useful in the future to provide us with more anatomical information in order to better understand the relationship between pathology of diverticular disease and its symptoms.

CHAPTER 8

Summary

8.1 SUMMARY

This thesis has evaluated the role of high frequency mini probe ultrasound in the assessment of different aspects of colorectal disease. It has clearly shown that mini probe ultrasound is feasible in the colon and rectum with minimal technical problems and without any undue complications. However, the various studies are only pilot in nature and further prospective research needs to continue with larger sample sizes in order to make more robust conclusions. This is a modality that involves some technical skill and is therefore subject to operator dependence and biases. Future studies should also include more than one ultrasound examiner with evaluation of inter-observer agreement keeping the blinded aspect of the study design. High frequency mini probes have been available for use for over 2 decades in the United Kingdom primarily in the upper gastrointestinal tract. It has not been adopted for routine use in the colon for a variety of reasons. The procedure is time consuming and on average each mini probe examination adds an additional 10 minutes to the colonoscopic examination. In addition, the examination requires deflating the colon of air and the instillation of water in the colon in order to achieve ultrasound coupling. The patient position may need to be altered from supine to right or left lateral or prone in order to allow for complete submersion of the pathology being scanned. Furthermore, utilisation of local staging of colonic pathology has not altered the course of patient management and there has therefore been slow uptake. Additionally, the ultrasound machine is expensive and the mini probes semi-disposable wearing on repeated use and rarely lasting more than 40 procedures. Each mini probe does have a cost attached to it and for this current thesis each mini probe was purchased at cost of £5000. This would add an additional £125 to each procedure if the probe lasted for 40 procedures. It is important to take care when handling the probes as they are mechanical radial probes which if bent or knocked may not function adequately. There are newer machines and probes on the market currently that cost the same, but last for several hundred procedures which is likely to be more cost effective (Fujinon variable frequency probe 7.5 MHz – 25 MHz). The added advantage of this later system is that all the probes are of variable frequency and therefore this saves time over changing probes regularly for change in frequencies.

Despite these observations, both 12 and 20 MHz ultrasound was superior to cross sectional imaging in local staging of colonic cancers and also more accurate than MRI in evaluation of the depth of invasion of rectal polyps. Although, local staging of colonic cancers is not currently an important aspect in the management of patients with resectable disease, this may gain more importance in the future if neo-adjuvant chemotherapy is adopted for locally advanced T3 and T4 tumours. This may gain further interest if the results of the UK FoXTROT study report in favour of neoadjuvant treatment. Interestingly, the 20 MHz ultrasound was able to detect subtleties such as invasion into the mucosa or submucosa with high accuracies of over 90%. 20 MHz ultrasound was utilised to assess rectal polyps prior to TEMS resection as all patients underwent surgery thereby providing histological comparison to the ultrasound staging. Further work is currently being undertaken within the department in the assessment of the depth of colonic polyps, potentially making this a suitable imaging modality to alter management of colorectal polyps as to whether they undergo endoscopic resection or standard surgical resection in the future

The assessment of the resection site after polypectomy of malignant lesions was shown to be feasible in the colon with evaluation of the presence of residual polyp and local lymphadenopathy. The direct comparison of ultrasonographic findings to histopathology was not feasible in all cases as only 6 patients underwent surgery. Nonetheless, all of the patients with normal ultrasound findings had normal histology with no presence of residual cancer in the specimen. This poses the question of whether ultrasound could be used in the future to guide us with management of malignant polyps. This question may have been better answered if sample size had been larger and all of the patients in the cohort had undergone surgery so direct comparison with histopathology could be made. Although the assessment of mesorectal nodes with ultrasound has been established in rectal tumours, there is no data regarding the assessment local lymph nodes after polypectomy in the colon. The ultrasound examination would be better suited prior to colonoscopic polypectomy but often the imaging is not available and incidental malignancy is often only noted after polypectomy on histology. Ultrasound criteria for positive lymph nodes also vary greatly from different units and often size is utilised as defining characteristic. However, all of this is subject to operator expertise and this is the main reason for such

variation in results. Nonetheless, it is worth pursuing as there is no clear consensus in the management of such patients and additional ultrasound information may help in the future to guide management.

Staging for local lymphadenopathy for colonic cancers or even in patients with malignant polyps has several limitations. Firstly, we are unable to predict the anatomical location of lymph nodes whether there are pericolic or mesenteric and also whether the nodes seen on ultrasound that are positive are indeed the same nodes that are deemed positive on histological examination. There is no method of confirming this unless you were able to mark or dye the node in endoscopically using ultrasound and then visualise the same staining on histopathology which seems rather far-fetched. There are 2 techniques which may be worth exploring in order to improve the diagnostic accuracy of local lymphadenopathy; ultrasound contrast agents and elastography.

The concept of ultrasound contrast agents was introduced by Gramiak and Shah (1967) who observed strong echo signals in blood after injection of indocyanine green as a result of air bubbles that were coadministered during the bolus injection. Since then the basis of ultrasound contrast agents is the intentional creation of air or gas bubbles. Contrast enhanced transabdominal ultrasound has been in place for over 10 years and has been shown to differentiate between benign and malignant liver tumours. The application of contrast agents to endoscopic ultrasound is relatively recent and this application is primarily to image the pancreas. Criteria for differentiation of pancreatic masses have been published (Dietrich 2008; Rickes 2002, 2004, 2007; D'Onofrio 2007). Adenocarcinomas are usually poorly vascularised whereas hypervascularisation after injection of a contrast agent is the characteristic sign of a neuroendocrine tumour and metastatic renal cell carcinomas. Studies evaluating this technology for the assessment of lymph nodes are few. There are only two studies in the literature which were performed to evaluate whether lymph nodes were benign or malignant (Kanamori 2006; Hocke 2008). The results were varied with sensitivity and specificity that ranged from 50% to 100% and from 71.8% to 81.8% respectively. Contrast enhanced colonoscopic ultrasound is an interesting concept and would be valuable in particular for assessment of lymph nodes in the follow up of patients having endoscopic surveillance for malignant polyps.

Elastography performed real time generates a visual scale of relative tissue hardness using a colour coded map superimposed on a B mode endorectal ultrasound image. The resulting elastogram is a product of a complex algorithm that states how tissues deform when pressure is applied rhythmically using a water filled balloon surrounding an ultrasound probe. Most real time elastography strain-ratio measurements provide semiquantitative data on relative tissue strain (Thomas 2010; Zhi 2008). Waage and colleagues (2010) have used endorectal elastography in the evaluation of rectal tumours. They obtained adequate elastography images in 66 out of their 69 patients in their series and identified an optimal strain ratio cut off value of 1.25 to discriminate between benign and malignant tumours, giving them a sensitivity, specificity and accuracy of 93%, 96% and 94% respectively. This technology could also be applied to assessment of lymph nodes and like contrast ultrasound may prove to be useful in assessing patients with malignant polyps. The greatest challenge, however, would be to apply this technology to the colon rather than just to the rectum.

Finally, the colonic wall thickness can be evaluated using 20 MHz ultrasound with consistently increased thickness of mucosa, submucosa and muscularis propria seen in patients with diverticular disease when compared with controls. This was particularly apparent for the muscularis propria with marked increase in thickness seen in diverticular disease patients. Further research needs to be focused in this area to determine whether there is any significance in the correlation of anatomical changes in diverticular disease with patient symptoms, in particular whether marked changes in thickness are present in symptomatic patients without many diverticula which may signify the 'pre-diverticular state'.

This thesis has outlined many of the advantages and some of the disadvantages of colonoscopic mini probe examination. Despite this, there has not been widespread uptake in this technique, the reasons of which have been discussed. The future of this technique lies in specialist tertiary referral centres in the assessment of colorectal polyps prior to endoscopic resection. Currently magnification colonoscopy is not widely available and mini probe ultrasound may be useful in identifying colorectal lesions that are mucosal and in the early submucosa which would be suitable for endoscopic mucosal resection and endoscopic submucosal dissection; and those that invade the deep submucosa which would be better treated with colorectal resection.

Mini probe ultrasound may take a limited role in the local staging of colonic cancers especially if the results of the FoXTROT study are favourable towards offering neoadjuvant chemotherapy for locally advanced colonic cancers. Although we have shown that local staging is superior with ultrasound compared to CT, ultrasound technology is likely to only be available in tertiary level centres and I suspect that emerging CT technology will provide better results which can easily applied across a national scale. We are still at earlier stages in the follow up of malignant polyps with colonoscopic ultrasound and there needs to be a larger study with longer follow up, but I suspect that this will receive much interest as it is often a surgical dilemma with regards to endoscopic surveillance versus surgery.

There are further developments in technology which may determine whether this will be adapted for assessment of lymph nodes such as Doppler, elastography and three dimensional ultrasound, the latter of which has just been developed but not been clinically assessed using mini probes.

LIST OF PUBLICATIONS

Haji A, Ryan S, Bjarnason I, Papagrigoriadis S. 20 MHz high frequency mini probe ultrasound as an aide to transanal endoscopic microsurgery (TEMS) – comparison with Magnetic Resonance Imaging (MRI). *Gut* 2009: Vol 58 (Suppl 1), p A84.

Haji A, Ryan S, Bjarnason I, Papagrigoriadis S. Prospective comparison of high frequency mini probe ultrasound and conventional computed tomography in the local staging of colonic cancers. *Gut* 2009: Vol 58 (Suppl 1), p A147.

Haji A, Ryan S, Bjarnason I, Papagrigoriadis S. High frequency ultrasound as a useful adjunct in the management of patients with malignant colorectal polyps. *Colorectal Disease* 2009: Vol 11 (Suppl 1), p8.

Haji A, Ryan S, Bjarnason I, Papagrigoriadis S. Colonoscopic high frequency ultrasound as a useful adjunct during routine colonoscopy. *Colorectal Disease* 2009: Vol 11 (Suppl 1), p14.

Haji A, Ryan S, Bjarnason I, Papagrigoriadis S. Prospective comparison of high frequency mini probe ultrasound and conventional computed tomography in the local staging of colonic cancers. *Colorectal Dis.* 2011 Nov 5. doi: 10.1111/j.1463-1318.2011.02871.x.

LIST OF PRESENTATIONS

- The use of colonoscopic ultrasound in the assessment of colonic tumours* Dec
2008
ACPGBI South East Chapter Meeting with RSM, Dartford
- High frequency mini probe ultrasound in the assessment of colonic wall thickness in diverticular disease*
Advances in diverticular disease, RSM, London Apr
2009
- Colonoscopic ultrasound as an adjunct to routine colonoscopy* May
2009
ASCRS, Hollywood, Florida, USA
- 20 MHz high frequency mini probe ultrasound as an aide to transanal endoscopic microsurgery (TEMS) – comparison with Magnetic Resonance Imaging (MRI).*
ACPGBI Annual Meeting, Harrogate June 2009
- Prospective comparison of high frequency mini probe ultrasound and conventional computed tomography in the local staging of colonic cancers.*
British Journal of Surgery Prize Session
ACPGBI Annual Meeting, Harrogate June 2009
- High frequency ultrasound as a useful adjunct in the management of patients with malignant colorectal polyps.*
ACPGBI Annual Meeting, Harrogate June 2009
- Colonoscopic high frequency ultrasound as a useful adjunct during routine colonoscopy. Video Presentation*
ACPGBI Annual Meeting, Harrogate June 2009
- Prospective comparison of high frequency mini probe ultrasound and conventional computed tomography in the local staging of colonic cancers.*
Colorectal Tripartite Meeting, Cairns, Australia July 2011
- 20 MHz high frequency mini probe ultrasound as an aide to transanal endoscopic microsurgery (TEMS) – comparison with Magnetic Resonance Imaging (MRI).*
Colorectal Tripartite Meeting, Cairns, Australia July 2011

LIST OF PRIZES

1. Prospective comparison of high frequency mini probe ultrasound and conventional computed tomography in the local staging of colonic cancers. British Journal of Surgery Prize for Best Paper, ACPGBI Annual Meeting, Harrogate, June 2009
2. Kings Development Award, Kings College London, Oct 2009
3. ASCRS Overseas Travelling Fellowship, May 2010
4. Royal Society of Medicine Coloproctology Travelling Fellowship June 2011

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APPENDIX 1

**PROTOCOLS, PATIENT INFORMATION LEAFLETS, CONSENT FORMS
AND LETTERS FOR ETHICS REVIEW**

**Protocol for research to assess the role of
colonoscopic ultrasound in the local staging of colonic
polyps and tumours**

Version 1.1

12/08/2007

1. Site of Study

Kings College Hospital

2.1 Principal Investigator

Mr S Papagrigoriadis
Consultant Colorectal Surgeon
Kings College Hospital

2.2 Investigators

Mr Aryn Haji
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Kings College Hospital

3. Background

Colorectal cancer is the third commonest cause of cancer related death in the United Kingdom and around 100 new cases of colorectal cancer are diagnosed each day in the United Kingdom. This amounts to nearly 17000 deaths (Cancer Research UK) per year. Current guidelines suggest that pre-operative staging of **colonic** cancers should include full imaging of the colon by way of a colonoscopy to confirm the tumour and exclude other synchronous lesions and also obtain biopsies for histological confirmation. Local and systemic pre-operative staging of the cancer is achieved by a Computerised Tomography (CT) scan of the abdomen, pelvis and chest. MRI and endoscopic ultrasound are being used routinely to assess the local spread of rectal cancers but have not found a place in colonic tumours.

Chemotherapy has an increasing role in the management of colorectal cancer and is currently offered in an adjuvant setting (post surgery) for colonic cancers that meet the criteria and as both a neo-adjuvant (pre-surgery) and adjuvant treatment for rectal cancers that meet the criteria. There is however much debate as to the role of neo-

adjuvant chemotherapy in the management of locally advanced colonic cancers. Currently, the FOXTROT national clinical trial has been designed to offer us more insight into this aspect of management of colonic tumours. The current assessment of locally advanced colonic cancers is by way of CT scan which is poor at assessing local disease and presence of local lymph nodes.

Endoscopic ultrasound has become the standard for pre-operative staging of cancers of the oesophagus, stomach and rectum but has not been used routinely for cancers of the colon. This has been due to the fact that up until now accurate pre-operative local staging information has not changed the management of patients with colonic tumours. However, with the introduction of endoscopic procedures for resection of early colonic cancers and the use of neo-adjuvant chemotherapy for locally advanced cancers, accurate local staging information is crucial in the pre-operative period similar to that with rectal cancers.

Endoscopic ultrasound is incorporated with the colonoscope to assess the tumour size, depth of infiltration and the presence or absence of local lymph nodes in the colonic mesentery. This has been shown to be 84-94% accurate in assessing depth of infiltration and 77-90% accurate in the assessment of local lymph nodes. However, the accuracy of endoscopic ultrasound as compared to conventional imaging using CT and histopathological analysis has not been prospectively evaluated in the literature.

This study will compare the local staging of colonic cancers by CT and endoscopic ultrasound using histopathological analysis of the resected specimen as the gold standard. The patients will undergo only their scheduled colonoscopy and shall have endoscopic ultrasound assessment of the colonic tumour during the same procedure. During the colonoscopy, if a colonic polyp is discovered, endoscopic ultrasound shall be used to assess the depth of invasion and lymph node status. Therefore, all patients scheduled for colonoscopy will be offered the opportunity to participate in the study.

Another arm of the study will examine staging of colonic malignant polyps which have been resected endoscopically and it is not known whether there is regional lymph nodes involvement. CT scan is an inaccurate investigation for evaluation of mesenteric lymph nodes and it is hoped that endoscopic ultrasound might offer better chance for detection. The detection of regional lymph nodes is essential to make a decision on whether further major surgery (colectomy) is necessary.

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4. Objective

To compare the accuracy of local staging of colonic tumours by CT scan and by colonoscopic ultrasound using histopathologic assessment of the specimen as gold standard

5. Materials and Method

5.1 Study population and Method

All patients who are offered colonoscopy at Kings College Hospital London will be invited to participate. Information leaflets shall be given to patients to take home at the time of the decision to book for endoscopy in the outpatient clinic. Informed consent will be taken for the procedure at the same time as consent for endoscopy on the day of procedure in only those patients who have received and read the information leaflets. In addition, patients discovered to have cancer within an excised colonic polyp will be identified from the Colorectal Multidisciplinary meetings and offered the opportunity to undergo an endoscopic ultrasound at their next scheduled colonoscopy.

Colonoscopic ultrasound shall only be performed in those patients in whom a colonic tumour or polyp is discovered. The ultrasound examination will take place during the same endoscopy using endoscopic ultrasound equipment already available within the department. The ultrasound image is obtained after instilling a small amount of water

in the colon similar to the water used to flush away debris in routine colonoscopy. The size of the tumour, depth of infiltration (T stage) and the presence of lymph nodes will be noted. Lymph nodes of all sizes shall be noted and measured. The ultrasound examination will increase the colonoscopy time by 5-10 minutes.

The management algorithm will not be affected by the ultrasound findings. Those patients who are discovered to have cancer of the colon will undergo their routine pre-operative investigations including CT scan of the abdomen / pelvis and chest. The diagnostic accuracy of the ultrasound will then be compared with CT and also with the pathological analysis of the resected specimen.

The CT scan will be assessed by a single Consultant Radiologist and the histological specimen will be analysed in the routine manner by the Colorectal Histopathologist at Kings College Hospital and discussed within the Colorectal multidisciplinary team.

The accuracy of local staging of colonic neoplasms by endoscopic ultrasound shall be compared with conventional CT with the pathological analysis of the resected specimen as the gold standard.

5.2 Exclusion criteria

- Patients from vulnerable groups (groups of patients in question A24 of COREC form3)

5.3 Study period

Recruitment for the study will be from October 2007. The study period will be for a period of 2 years.

5.4 Data Protection

The data will consist of documents and computer files. Documents will be stored in a locked office in the Department of Colorectal Surgery. Computer files will be password protected and exist on a computer in the same office. Data will be maintained as per Data Protection Act 1984.

5.5 Data Analysis

All data will be expressed as mean \pm standard deviation or percentage. Student's *t*-test and chi-squared test will be used for statistical analysis, with the level of statistical significance set at $P < 0.05$.

6. Results

The results of the study will aim to assess the accuracy of local staging of colonic polyps and tumours by colonoscopic ultrasound, conventional CT and compare these to the histological examinations of the resected specimens. We hope to show the superiority of colonic ultrasound over conventional CT

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CONSENT FORM (Version 1.1 (12/08/2007))

Title of project: The use of colonoscopic ultrasound to assess colonic tumours

**Investigators: Mr Savvas Papagrigoriadis, Mr Aryn Haji, Dr Suzanne Ryan
Dr John Devlin, Dr David Reffitt, Professor Ingvar Bjarnason**

Researcher obtaining consent:

Name Signature

To be completed by the volunteer

Circle as Necessary

1. Have you read the information sheet about this study? YES/ NO
2. Have you had the opportunity to ask questions and discuss the study? YES/ NO
3. Have you received satisfactory answers to all your questions? YES/ NO
4. Have you received enough information about this study? YES/ NO
5. Do you understand that you are free to withdraw from this study and ask for your
information to be destroyed?
*at any time
*without giving a reason
*without affecting your future medical care or legal rights YES/ NO
6. Do you agree to your General Practitioner being informed about your participation in this
study? YES/ NO
7. I understand that relevant sections of my medical notes and data collected during the study
may be looked at by the research investigators and that the data will be confidential and used
only for research purposes YES/ NO
8. Do you agree to take part in this study? YES/ NO

.....
Name of patient

.....
Date

.....
Signature

PATIENT INFORMATION SHEET - Version 1.1 (12/08/2007)

Title of project: The use of colonoscopic ultrasound to assess colonic tumours

**Investigators: Mr Savvas Papagrigoriadis, Mr Aryn Haji
Dr John Devlin, Dr Suzanne Ryan**

As a patient of Kings College Hospital we invite you to participate in this research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully.

You do not have to take part in this study if you do not want to. If you decide to take part you may withdraw at any time without giving a reason. Your decision whether to take part or not will not affect your care and management in any way.

Introduction

This information sheet is being given to all patients who have been advised by their doctor to have a form of bowel investigation called Colonoscopy. This investigation involves a camera that looks at the inner lining of the large bowel. The leaflet will explain about the research project and provide information to help you make up your mind about participation. Detailed information about colonoscopy is also included separately in the pack.

Colorectal cancer is the third commonest cause of cancer related death in the United Kingdom and around 100 new cases of colorectal cancer are diagnosed each day in the United Kingdom. Currently, if there is a growth detected in the bowel routine investigations are performed to check whether this is a cancer or a benign growth. All patients would normally have a colonoscopy and a CT scan of the abdomen. A scan of the growth can also be done from inside the bowel at the same time as the colonoscopy using a ultrasound probe which is attached to the colonoscope. Ultrasound is commonly used and you or a family member may have had a scan before. This has been shown to be very good at detecting growths in the bowel and has the advantage of being done at the same time as the colonoscopy.

What is involved?

The ultrasound scan will take place during your colonoscopy using a mini ultrasound probe attached to the colonoscope. This examination only occurs during the colonoscopy if the consultant finds any growths in the bowel, and will not affect the way you feel during the colonoscopy. However, it will increase the time taken to complete the colonoscopy by 5-10 minutes. During the scan, some water may be placed into the bowel for the scan to give better pictures. We sometimes flush water into the bowel during a routine colonoscopy so that we can see better and this does not

cause any irritation to the bowel, nor will you feel any discomfort while this is happening.

You will only be asked to have this scan only once at the same time of your scheduled colonoscopy. There will be no additional investigations done for the study unless it is indicated for the management of your condition.

What data will be collected?

The ultrasound scan image will give us information about how deep the growth in the bowel is and whether there are any lymph glands surrounding the growth outside the bowel.

The information gathered from this research will then be used to compare the accuracy of colonoscopic ultrasound with that of a routine CT scan of the abdomen. This will then be able to direct different treatments in the future for patients with colonic cancers and benign growth.

What are the possible risks and disadvantages of taking part in the research?

Ultrasound has been routinely used in medicine and we are not aware of any potential risks from its use. However, as the scan will take a few minutes to perform, this will increase your colonoscopy time by 5-10 minutes.

Protection of information and confidentiality

All the information we obtain will be strictly confidential. Only study investigators (named above) will have access to the data stored within double password-protected databases within a locked office. We are required to keep the data for a minimum of 2 years after the study has been completed. Information about you is bound by the regulations of medical confidentiality and will not be made available to outside organisations or insurance companies.

For any further information or concerns regarding the study please contact

Mr Aryn Haji
Clinical Research Fellow in Colorectal Surgery
Kings College Hospital
Denmark Hill SE5 9RS

Tel: 0207 346 4667
Email: amyn.haji@kcl.nhs.uk

Letter to General Practitioner - Version 1.1 (12/08/2007)

Title of project: The use of colonoscopic ultrasound to assess colonic tumours

**Investigators: Mr Savvas Papagrigoriadis, Mr Aryn Haji
Dr John Devlin, Dr Suzanne Ryan**

Dear Doctor

Patient Name :

Hospital No.

Date of Birth :

This letter is to inform you that the above patient has volunteered to participate in a clinical research project at Kings College Hospital. I have enclosed a copy of the information leaflet and protocol for your information.

Please do not hesitate to contact me if you have any further queries.

Kind regards

Aryn Haji MA MBBChir MRCS
Colorectal Research Fellow
Kings College Hospital
Denmark Hill
London
SE5 9RS

Tel. 0207 346 4667
amyn.haji@kcl.nhs.uk

**Protocol for research to assess the use of
colonoscopic ultrasound in the assessment of
diverticular disease**

Version 1.1

19/09/2007

1. Site of Study

Kings College Hospital

2.1 Principal Investigator

Mr S Papagrigoriadis
Consultant Colorectal Surgeon
Kings College Hospital

2.2 Investigators

Mr Aryn Haji
Colorectal Research Fellow
Kings College Hospital

Dr Suzanne Ryan
Consultant Radiologist
Kings College Hospital

Dr John Devlin
Consultant Hepatologist
Kings College Hospital

3. Background

Diverticular disease is an increasingly common benign disease of the colon which causes significant morbidity and mortality.

The colon in diverticular disease appears shortened with a thickened muscular wall, redundant mucosal folds, and diverticula disposed in two to four parallel longitudinal rows between the mesenteric and the antimesenteric teniae. The longitudinal and circular muscle in the teniae appears thickened (Whiteway and Morson 1985; M J Ford 1995).

There is an abnormality of muscularis propria in diverticular disease leading to its shortening and thickening, causing it to behave like myostatic contracture (Morson 1963). The consequent plication of the circular layer narrows the lumen, thus increasing the intraluminal pressure according to Laplace's law. The resulting hypersegmentation is thought to be important in the pathogenesis of the diverticula (Painter 1969).

The primary muscle abnormality leading to a non-compliant wall seems to be due to mychosis and the intrinsic derangement of collagen fibres (Thomson, Busuttil et al. 1987). Mychosis refers to the progressive elastosis of the taenia coli attributed to the increased proline in the western diet (Whiteway and Morson 1985). Abnormalities in increased collagen deposition and cross linking are also implicated in decreased colonic tensile strength (Wess L 1995; Wess L 1996).

Left-sided diverticula occur most often in the sigmoid colon, which has the smallest diameter, lowest compliance and therefore the highest intraluminal pressures (Waldron et al, 1989, Ford et al, 1995). Not only do patients with diverticular disease have higher colonic intraluminal pressures than control subjects (Painter & Truelove, 1964, Arfwidsson et al, 1964, Parks, 1970, Shafik et al, 2004, Trotman et al, 1988), but it has also been shown that basal and post prandial intraluminal pressures are higher in patients with symptomatic diverticular disease compared to those with asymptomatic diverticular disease. (Cortisini & Pantalone, 1991). The motility patterns in diverticular disease show similarity to those of Irritable Bowel Syndrome (IBS) to the extent that some researchers have suggested that the two conditions may be two forms of the same.

Serotonin (5-HT) is 3-(β -aminoethyl)-5-hydroxyindole. The gut contains over 95% of the body's 5-HT (Gershon MD et al, 1977, Erspamer V, 1967). Enteric neurones synthesize 5-HT and store it. Serotonin has been found to be increased in the colonic mucosa of resected specimens in patients with diverticular disease (Banerjee, Akbar et al. 2007). This relates to the increased colonic motility seen in diverticular disease. Therefore serotonin antagonists may have a role in slowing progression of this disease and also reducing symptoms, particularly in those patients whose predominant symptom is diarrhoea. Current research in the department at Kings College Hospital suggests that an increased concentration of serotonin is present in patients with worsening symptoms relating to diverticular disease.

Currently, patients suspected to have diverticular disease are investigated using colonoscopy and Computerised Tomography of the abdomen and pelvis. Neither of these investigations are accurate in the assessment of bowel wall thickness. Endoscopic ultrasound has become the standard for pre-operative staging of cancers of the oesophagus, stomach and rectum but has not been used in the routine evaluation of benign colonic conditions. This study will assess the bowel wall thickness in patients with diverticular disease and correlate these findings with their symptoms. In addition, the findings will also be correlated with the levels of serotonin observed in the colonic mucosa.

It is hoped that the colonoscopic ultrasound findings will aid in the future selection of patients suitable for elective surgery with symptomatic diverticular disease

4. Objective

- To assess the thickness of bowel wall in patients with symptomatic and asymptomatic Diverticular Disease
- To develop a link between bowel wall thickness with relation to patients symptoms and levels of Serotonin on mucosal biopsy

5. Materials and Method

5.1 Study population and Method

All patients with diverticular disease will be eligible for entry into the study. Colonoscopy will be performed only for appropriate clinical reasons. Patients will not undergo any additional investigations. Participants with the following colonoscopic diagnosis will be recruited:

- a) Asymptomatic Diverticular disease
- b) Symptomatic Diverticular disease
- c) Patients with complicated diverticular disease requiring further assessment
i.e: strictures, pericolic abscess, fistulae

A sample size will be calculated based on results from the pilot study. Approximately three groups of twenty patients will be participants.

5.4 Exclusion criteria

- Patients from vulnerable groups (groups of patients in question A24 of COREC form3)

5.5 Study period

Recruitment for the study will be from October 2007. The study period will be for a period of 2 years.

5.4 Data Protection

The data will consist of documents and computer files. Documents will be stored in a locked office in the Department of Colorectal Surgery. Computer files will be password protected and exist on a computer in the same office. Data will be maintained as per Data Protection Act 1984.

5.5 Data Analysis

All data will be expressed as mean \pm standard deviation or percentage. Student's *t*-test and chi-squared test will be used for statistical analysis, with the level of statistical significance set at $P < 0.05$. In addition further analyses using statistical models with logistic regression and artificial neural networks.

6. Results

The results of the study will aim to primarily assess the thickness of bowel wall in asymptomatic and symptomatic diverticular disease. This will be in turn be correlated with levels of serotonin in mucosal biopsies and patients' symptomology.

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CONSENT FORM (Version 1.1 (19/09/2007))

Title of project: The use of colonoscopic ultrasound to assess diverticular disease

**Investigators: Mr Savvas Papagrigoriadis, Mr Aryn Haji, Dr Suzanne Ryan
Dr John Devlin, Dr David Reffitt, Professor Ingvar Bjarnason**

Researcher obtaining consent:

Name Signature

To be completed by the volunteer

Circle as Necessary

1. Have you read the information sheet about this study? YES/ NO
2. Have you had the opportunity to ask questions and discuss the study? YES/ NO
3. Have you received satisfactory answers to all your questions? YES/ NO
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5. Do you understand that you are free to withdraw from this study and ask for your
information to be destroyed?
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*without affecting your future medical care or legal rights YES/ NO
6. Do you agree to your General Practitioner being informed about your participation in this
study? YES/ NO
7. I understand that relevant sections of my medical notes and data collected during the study
may be looked at by the research investigators and that the data will be confidential and used
only for research purposes YES/ NO
8. Do you agree to take part in this study? YES/ NO

.....
Name of patient

.....
Date

.....
Signature

PATIENT INFORMATION SHEET - Version 1.1 (19/09/2007)

Title of project: The use of colonoscopic ultrasound to assess diverticular disease

**Investigators: Mr Savvas Papagrigoriadis, Mr Aryn Haji, Dr Suzanne Ryan
Dr John Devlin, Dr David Reffitt**

As a patient of Kings College Hospital we invite you to participate in this research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully.

You do not have to take part in this study if you do not want to. If you decide to take part you may withdraw at any time without giving a reason. Your decision whether to take part or not will not affect your care and management in any way.

Introduction

The following relates to a research project being undertaken at King's College Hospital. The information sheet is being given to all patients who have been advised by their doctor to have a form of bowel investigation called Colonoscopy. This investigation involves a camera that images the inner lining of the large bowel. The leaflet will explain about the research project and provide information to help you make up your mind about participation. Information about Colonoscopy is included separately in the pack.

Diverticular Disease is a condition that affects the large bowel. It is a common condition affecting approximately 70% of people over the age of seventy. It also affects younger age groups. Diverticular disease occurs when the inner lining of the large bowel balloons through the outer wall of the bowel. This is thought to occur from high pressure within the bowel forcing the inner lining to balloon out. The condition is essentially progressive – the longer the duration the worse the symptoms and the greater risk of complications. This may cause symptoms of distension, flatulence and a sense of heaviness in the lower abdomen. It is not a condition that leads to cancer, but cancers may co-exist.

Currently, if there is diverticular disease suspected in the bowel and you are having increasing symptoms from this, routine investigations are performed to check for any complications from the diverticular disease and to exclude other conditions which may cause similar symptoms. All patients would normally have a colonoscopy and a CT scan of the abdomen. A scan of the bowel can also be done from inside the bowel at the same time as the colonoscopy using an ultrasound probe which is attached to the colonoscope. This has been shown to be very accurate at measuring the thickness of

the bowel wall and has the advantage of being done at the same time of the colonoscopy.

What is involved?

The ultrasound scan will take place during your colonoscopy using a mini ultrasound probe attached to the colonoscope. This examination only occurs during the colonoscopy if the consultant finds any diverticular disease in the bowel, and will not affect the way you feel during the colonoscopy. During the scan, some water may be placed into the bowel for the scan to give better pictures. We sometimes flush water into the bowel during a routine colonoscopy so that we can see better and this does not cause any irritation to the bowel, nor will you feel any discomfort while this is happening.

You will only be asked to have this scan only once at the same time of your scheduled colonoscopy. There will be no additional investigations done for the study unless it is indicated for the management of your condition.

What happens if I have diverticular disease?

You will be offered expert advice regarding the condition and be offered the opportunity to visit a specialist clinic at Kings College Hospital which is already in place. Here you will have the opportunity to discuss your symptoms and plan treatment if necessary

What data will be collected?

The ultrasound scan images will be used to measure the thickness of the bowel wall in diverticular disease. The results may lead to better understanding of Diverticular Disease. It may also increase the probability of detecting complications of diverticular disease.

What are the possible risks and disadvantages of taking part in the research?

Ultrasound has been routinely used in medicine and we are not aware of any potential risks from its use. However, as the scan will take a few minutes to perform, this will increase your colonoscopy time by 5-10 minutes.

Protection of information and confidentiality

All the information we obtain will be strictly confidential. Only study investigators (named above) will have access to the data stored within double password-protected databases within a locked office. We are required to keep the data for a minimum of 2 years after the study has been completed. Information about you is bound by the regulations of medical confidentiality and will not be made available to outside organisations or insurance companies.

For any further information or concerns regarding the study please contact:

Mr Amyn Haji
Clinical Research Fellow in Colorectal Surgery
Kings College Hospital
Denmark Hill SE5 9RS
Tel: 0207 346 4667
Email: amyn.haji@kcl.nhs.uk

Letter to General Practitioner - Version 1.1 (19/09/2007)

Title of project: The use of colonoscopic ultrasound to assess diverticular disease

**Investigators: Mr Savvas Papagrigoriadis, Mr Aryn Haji
Dr John Devlin, Dr Suzanne Ryan**

Dear Doctor

Patient Name

Hospital No.

Date of Birth

This letter is to inform you that the above patient has volunteered to participate in a clinical research project at Kings College Hospital. I have enclosed a copy of the information leaflet and protocol for your information.

Please do not hesitate to contact me if you have any further queries.

Kind regards

Aryn Haji MA MBBChir MRCS
Colorectal Research Fellow
Kings College Hospital
Denmark Hill
London
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Tel. 0207 346 4667
amyn.haji@kcl.nhs.uk

APPENDIX 2 – QUALITY OF LIFE QUESTIONNAIRES

1. Diverticular disease – Quality of life questionnaire (Guyatt)
2. SF-36 Questionnaire

Diverticular Disease – Quality of Life Questionnaire (Guyatt)

The following questionnaire includes 32 questions which are grouped into four categories – bowel symptoms (B), systemic symptoms (S), emotional functions (E) and social functions (SF).

Response options are presented as a seven-point scale where number 1 on the scale is the most frequent /troublesome and number 7 is no problem/normal. Please circle the most appropriate option.

For example

No 1. How frequent have your bowel movements been during the last two weeks?

Options

1. Bowel movements as or more frequent than they have ever been
2. extremely frequent
3. very frequent
4. moderate increase in frequency of bowel movements
5. some increase in frequency of bowel movements
6. slight increase in frequency of bowel movements
7. normal, no oncrease in frequency of bowel movements

1 2 3 4 5 6 7

Date

Hospital number

Date of birth

Date and type of surgery if any

(B) 1. How frequently have your bowel movements been during the last two weeks?

1 2 3 4 5 6 7

(S) 2. How often has the feeling of fatigue or being tired and worn out been a problem for you in the last two weeks?

1 2 3 4 5 6 7

(E) 3. How often during the last two weeks have you felt frustrated, impatient or restless?

1 2 3 4 5 6 7

(SF) 4. How often during the last two weeks have you been unable to attend work or undertake every day activities because of your bowel problem?

1 2 3 4 5 6 7

(B) 5. How much of the time during the last two weeks have your bowel movements been loose?

1 2 3 4 5 6 7

(S) 6. How much of energy have you had during the last two weeks?

1 2 3 4 5 6 7

(E) 7. How often during the last two weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem?

1 2 3 4 5 6 7

(SF) 8. How often during the last two weeks have you had to delay or cancel a social engagement because of your bowel problem?

1 2 3 4 5 6 7

(B) 9. How often during the last two weeks have you been troubled by cramps in your abdomen?

1 2 3 4 5 6 7

(S) 10. How often during the last two weeks have you felt generally unwell?

1 2 3 4 5 6 7

(E) 11. How often during the last two weeks have you been troubled because of fear of not finding a washroom?

1 2 3 4 5 6 7

(SF) 12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last two weeks?

1 2 3 4 5 6 7

(B) 13. How often during the last two weeks have you been troubled by pain in the abdomen?

1 2 3 4 5 6 7

(S) 14. How often during the last two weeks have you had problems getting a good nights sleep, or been troubled by waking up in the night?

1 2 3 4 5 6 7

(E) 15. How often during the last two weeks have you felt depressed or discouraged?

1 2 3 4 5 6 7

(SF) 16. How often during the last two weeks have you had to avoid attending events where there was no washroom close at hand?

1 2 3 4 5 6 7

(B) 17. Overall in the last two weeks, how much of a problem have you had with passing large amounts of gas?

1 2 3 4 5 6 7

(S) 18. Overall in the last two weeks, how much of a problem have you had maintaining, or getting to, the weight you would like to be at?

1 2 3 4 5 6 7

(E) 19. Many patients with bowel problems often have worries and anxieties relating to their illness. These include worries about getting cancer, worries about never feeling any better and worries about having a relapse. In general, how often during the last two weeks have you felt worried or anxious?

1 2 3 4 5 6 7

(B) 20. How much of time during the last two weeks have you been troubled by a feeling of abdominal bloating?

1 2 3 4 5 6 7

(E) 21. How often during the last two weeks have you felt relaxed and free from tension?

1 2 3 4 5 6 7

(B) 22. How much of the time during the last two weeks have you had a problem with rectal bleeding with your bowel movements?

1 2 3 4 5 6 7

(E) 23. How much of time during the last two weeks have you felt embarrassed as a result of your bowel problem?

1 2 3 4 5 6 7

(B) 24. How much of the time during the last two weeks have you been troubled by a feeling of having to go the bathroom even though your bowels are empty?

1 2 3 4 5 6 7

(E) 25. How much time during the last two weeks have you felt tearful or upset?

1 2 3 4 5 6 7

(B) 26. How much of the time during the last two weeks have you been troubled by accidental soiling of your underpants?

1 2 3 4 5 6 7

(E) 27. How much of the time during the last two weeks have you felt angry as a result of your bowel problem?

1 2 3 4 5 6 7

(SF) 28. To what extent had your bowel problem limited sexual activity during the last two weeks?

1 2 3 4 5 6 7

(B) 29. How much of the time during the last two weeks have you been troubled by feeling sick to your stomach?

1 2 3 4 5 6 7

(E) 30. How much of the time during the last two weeks have you felt irritable?

1 2 3 4 5 6 7

(E) 31. How often during the last two weeks have you felt a lack of understanding from others?

1 2 3 4 5 6 7

(E) 32. How satisfied, happy or pleased have you been with your personal life during the past two weeks?

1 2 3 4 5 6 7

Thank you for completing this questionnaire

Mr Aryn Haji

Clinical Research Registrar in Colorectal Surgery

Kings College Hospital

SF36 Health Survey

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.			
1.	In general, would you say your health is: (Please tick one box.) Excellent <input type="checkbox"/> Very Good <input type="checkbox"/> Good <input type="checkbox"/> Fair <input type="checkbox"/> Poor <input type="checkbox"/>		
2.	Compared to one year ago, how would you rate your health in general <u>now</u> ? (Please tick one box.) Much better than one year ago <input type="checkbox"/> Somewhat better now than one year ago <input type="checkbox"/> About the same as one year ago <input type="checkbox"/> Somewhat worse now than one year ago <input type="checkbox"/> Much worse now than one year ago <input type="checkbox"/>		
3.	The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much? (Please circle one number on each line.)		
	Activities	Yes, Limited A Lot	Yes, Limited A Little
3(a)	Vigorous activities , such as running, lifting heavy objects, participating in strenuous sports	1	2
3(b)	Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2
3(c)	Lifting or carrying groceries	1	2
3(d)	Climbing several flights of stairs	1	2
3(e)	Climbing one flight of stairs	1	2
3(f)	Bending, kneeling, or stooping	1	2
3(g)	Walking more than a mile	1	2
3(h)	Walking several blocks	1	2
3(i)	Walking one block	1	2
3(j)	Bathing or dressing yourself	1	2
4.	During the <u>past 4 weeks</u> , have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u> ? (Please circle one number on each line.)		
		Yes	No
4(a)	Cut down on the amount of time you spent on work or other activities	1	2
4(b)	Accomplished less than you would like	1	2
4(c)	Were limited in the kind of work or other activities	1	2
4(d)	Had difficulty performing the work or other activities (for example, it took extra effort)	1	2
5.	During the <u>past 4 weeks</u> , have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (e.g. feeling depressed or anxious)? (Please circle one number on each line.)		
		Yes	No
5(a)	Cut down on the amount of time you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box.)

Not at all ☐
 Slightly ☐
 Moderately ☐
 Quite a bit ☐
 Extremely ☐

7. How much physical pain have you had during the past 4 weeks? (Please tick **one** box.)

None ☐
 Very mild ☐
 Mild ☐
 Moderate ☐
 Severe ☐
 Very Severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

Not at all ☐
 A little bit ☐
 Moderately ☐
 Quite a bit ☐
 Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.

(Please circle one number on each line.)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9(a) Did you feel full of life?	1	2	3	4	5	6
9(b) Have you been a very nervous person?	1	2	3	4	5	6
9(c) Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d) Have you felt calm and peaceful?	1	2	3	4	5	6
9(e) Did you have a lot of energy?	1	2	3	4	5	6
9(f) Have you felt downhearted and blue?	1	2	3	4	5	6
9(g) Did you feel worn out?	1	2	3	4	5	6
9(h) Have you been a happy person?	1	2	3	4	5	6
9(i) Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box.)

All of the time ☐
 Most of the time ☐
 Some of the time ☐
 A little of the time ☐
 None of the time ☐

11. How TRUE or FALSE is each of the following statements for you?

(Please circle one number on each line.)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
11(a) I seem to get sick a little easier than other people	1	2	3	4	5
11(b) I am as healthy as anybody I know	1	2	3	4	5
11(c) I expect my health to get worse	1	2	3	4	5
11(d) My health is excellent	1	2	3	4	5

Thank You!